Michael S. Ritsner *Editor*

Handbook of Schizophrenia Spectrum Disorders

Volume III

Therapeutic Approaches, Comorbidity, and Outcomes

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Foreword

Schizophrenia Spectrum Disorders: Insights from Views Across 100 years

Schizophrenia spectrum and related disorders such as schizoaffective and mood disorders, schizophreniform disorders, brief psychotic disorders, delusional and shared psychotic disorders, and personality (i.e., schizotypal, paranoid, and schizoid personality) disorders are the most debilitating forms of mental illness, worldwide. There are 89,377 citations (including 10,760 reviews) related to "schizophrenia" and 2118 (including 296 reviews) related to "schizophrenia spectrum" in PubMed (accessed on August 12, 2010).

The classification of these disorders, in particular, of schizophrenia, schizoaffective and mood disorders (referred to as functional psychoses), has been debated for decades, and its validity remains controversial. The limited success of genetic studies of functional psyhoses has raised questions concerning the definition of genetically relevant phenotypes.

Many researchers around the world have investigated schizophrenia spectrum, and related disorders from the perspectives of diagnostics, early detection of psychotic disorders, genetics, neuroscience, prognosis, and treatment. Therefore, these

fields have considerably expanded with new findings that were obtained through clinical and longitudinal observations and neuropsychological, neurophysiological, neuroimaging, neuroanatomical, neurochemical, molecular genetic, genomic and proteomic analyses, which have generated a necessity for syntheses across the functional psychoses.

The present three-volume handbook is a collection that continues to achieve my goal of providing a comprehensive up-to-date state of the art overview of the literature that addresses the challenges facing clinical and biological psychiatry. This series follows four recently published books:

- *Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders. New Perspectives on Research and Treatment.* Ritsner, Michael S.; Awad, A. George (Eds.), Springer, 2007, 388p.
- *Neuroactive Steroids in Brain Functions, and Mental Health. Novel Strategies for Research and Treatment.* Ritsner, Michael S.; Weizman A. (Eds.), Springer Science+Business Media, B.V., 2008. 559p.
- *The Handbook of Neuropsychiatric Biomarkers, Endophenotypes, and Genes. Volumes I–IV.* Ritsner, Michael S. (Ed.), Springer Science+Business Media, B.V., 2009.

  Volume I: Neuropsychological Endophenotypes and Biomarkers. 231pp.
  Volume II: Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers. 244pp.
  Volume III: Metabolic and Peripheral Biomarkers. 231pp.
  Volume IV: Molecular Genetic and Genomic Markers. 232pp.

- *Brain Protection in Schizophrenia, Mood and Cognitive Disorders.* Ritsner, Michael S. (Ed.), Springer Science+Business Media, B.V., 2010. 663 p.

This handbook offers a broad synthesis of current knowledge about schizophrenia spectrum and related disorders. It is based on methodological pluralism regarding psychiatric nosology and raises many controversial issues, and limitations of categorical nosology of functional psychoses covering the ongoing debate on key conceptual issues that may be relevant for the development of DSM-V and ICD-11.

Reflecting the copious amount of new information provided, the handbook has been divided *into three volumes*. *Volume I* contains 20 chapters and serves as an introduction and *overview of theoretical issue, and neurobiological advances*. The chapters in this volume review the schizophrenia construct, diagnosis and classification of the schizophrenia spectrum disorders, and schizotypy concept; present proof-of-concept Multidimensional Continuum Model of functional psychoses and evolutionary models of autism; new findings regarding neurodevelopmental, neurodegenerative, and neurochemical abnormalities; genetic and environmental influences; changes in gene expression; neurotransmitter activity; brain imaging and morphological abnormalities in subjects with schizophrenia and other psychotic disorders, methamphetamine psychosis as a model for biomarker discovery

in schizophrenia and advances in proteomics. Our knowledge of the genetics of schizophrenia and its borderlands is heavily indebted to the research and writings of *Professor Irving Gottesman*. The chapter that summarizes his contributions in that historical context is an invaluable contribution to the handbook.

Volume II contains 19 chapters focusing on *phenotypic and endophenotypic presentations* of schizophrenia spectrum and related disorders. The authors discuss psychopathology, stress, social anxiety, neuropsychological, neurocognitive and neurophysiological findings, endophenotype and neuroethological approaches, quality of life deficits, and risk for cancer morbidity and mortality. The authors also review advances and *challenges* in mapping the prodromal phases of psychosis, in the prediction and early detection of first-episode psychosis, early- and late-onset schizophrenia, the longitudinal course of these disorders, as well as the interface of acute transient psychoses, the association of metacognition with neurocognition and function in schizophrenia, neurophysiology of cognitive dysfunction in schizophrenia, schizo-obsessive states, and risk for cancer morbidity and mortality in schizophrenia spectrum disorders.

Volume III includes 18 chapters that provide a wealth of information regarding treatment approaches, comorbidity, recovery, and outcomes of schizophrenia and spectrum disorders; in particular, recovery-based treatment approaches, antipsychotic and neuroprotective-based treatment; prevention and early intervention in at-risk states for developing psychosis, psychotherapy, cognitive remediation, cognitive behavior therapy; and interventions targeting social and vocational dysfunction in schizophrenic spectrum disorders. Furthermore, therapeutic approaches to schizophrenia with medical illness, comorbid substance abuse, suicidality, implications for treatment and community support, the relationship between religiosity/spirituality and schizophrenia, and the ethical ramifications of biomarker use for mood disorders are also reviewed and discussed.

Since many of the contributors to this handbook are internationally known experts, they not only provide up-to-date state of the art overviews, but also clarify some of the ongoing controversies and future challenges and propose new insights for future research. The contents of these volumes have been carefully planned, organized, and edited. Of course, despite all the assistance provided by contributors, I alone remain responsible for the content of this handbook including any errors or omissions which may remain. Similar to other publications contributed to by diverse scholars from diverse orientations and academic backgrounds, differences in approaches and opinions, as well as some overlap, are unavoidable.

This handbook is designed for use by a broad spectrum of readers including psychiatrists, neurologists, neuroscientists, endocrinologists, pharmacologists, psychologists, general practitioners, geriatricians, graduate students, and health care providers in the fields of mental health. It is hoped that this book will also be a useful resource for the teaching of psychiatry, neurology, psychology and policy makers in the fields of mental health.

I would like to gratefully acknowledge all contributors from 16 countries (Australia, Brazil, Canada, China, Czech Republic, Denmark, Germany, Ireland, Italy, Israel, Japan, Spain, Switzerland, Ukraine, United Kingdom, and USA)

for their excellent cooperation. I wish to thank *Professor William T. Carpenter*, distinguished psychiatrist, who was willing to write the afterword for this handbook. I also wish to take this opportunity to thank the wonderful staff in my clinical department as well as in other departments in Shaar-Menashe Mental Health Center (Director – Dr. Alexander Grinshpoon) for their commitment, support, and cooperation. I would like to thank my wonderful and generous friends, particularly Boris Altshuler, Anatoly Polischuck, and Stella Lulinsky. They always took the time to listen, even when I was just complaining. The support they have given me over the years is the greatest gift anyone has ever given me. Finally, I thank Springer Science Business Media B.V. for the goodwill and publication of this book, particularly Mr. Peter Butler, and Dr. Martijn Roelandse, publishing editors, who did their utmost to promote this project and provided valuable assistance that made the book possible.

I sincerely hope that this handbook will further knowledge in the complex field of psychiatric disorders.

Haifa, Israel
March, 2011

Michael S. Ritsner

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Chapter 1
Recovery in Schizophrenia: Perspectives, Evidence, and Implications

Anthony O. Ahmed, P. Alex Mabe, and Peter F. Buckley

Abstract The recovery model of schizophrenia represents a paradigm shift in both the conceptualization and treatment of schizophrenia. However, the varied use of the term "recovery" in research and clinical settings has caused confusion about what it means in relation to schizophrenia. Two views of recovery appear in the literature including a medical model, having its origins in treatment outcome studies; and a consumer model of recovery, which was conceived from the writing and testimonials of former patients. The medical model of recovery suggests that there are many possible outcomes in the prognosis of schizophrenia and many patients do experience periods of symptom remission and improved functioning. On the other hand, the consumer model of recovery suggests that recovery involves integrating illness into a multifaceted sense of self that actively pursues goals, interests, roles, and aspirations despite the limitations imposed by the illness. This model emphasizes hope, empowerment, and overall wellness regardless of the status of symptoms and functional disability. The current chapter is an overview of the medical and consumer views of recovery and studies supporting both models. Despite their distinct origins and focus, both models of recovery offer a hopeful view of recovery in schizophrenia; however, implementing the consumer model of recovery in mental health systems is freight with challenges.

Keywords Schizophrenia · Recovery · Outcome · Process

Abbreviations

Project GREAT	Georgia Recovery-based Educational Approach to Treatment
SAMHSA	The Substance Abuse and Mental Health Services Administration

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Introduction

In the last two decades, the concept of recovery in schizophrenia has emerged as an essential construct in the study and treatment of schizophrenia and schizophrenia spectrum disorders. Traditionally, "recovery" has primarily being viewed as an outcome characterized by symptom mitigation or reduction and improvements in functional capacities. This view draws from the medical model, which underscores the symptomatic experience of psychiatric illnesses and the role of targeted interventions to decrease symptoms and disabilities. Historically, schizophrenia had been viewed as a chronic condition marked by poor functional and therapeutic outcomes. With evidence emerging from recent studies of short-term and long-term outcomes, this view has evolved into one of a more positive medical conception of recovery. Current views of schizophrenia characterize the disorder as having a more, heterogeneous symptom course, including periods of good functioning for many patients. Emanating from a mental consumer/survival movement is a new paradigm for the concept of recovery. This consumer/survival perspective views recovery as a process rather than an outcome, and thus deemphasizes the role of symptom remission. Moreover, this paradigm of recovery focuses on the individual as a "whole person" with personal attributes and capacities and reframes the process of care around the individual's long-term expectations and lifetime aspirations. Central to this view of recovery is the instillation of hope and empowerment, and a development of a self living a full life despite the limitations of illness.

Both perspectives are considerably independent, having distinct origins, focus, and ramifications for assessment, treatment planning, and research in schizophrenia spectrum disorders. The current chapter examines these divergent recovery constructs in schizophrenia. We begin with a conceptual review of the medical and consumer perspectives of recovery including research evidence pertinent to both views of recovery. We then discuss the implications of the consumer model of recovery.

What Is Recovery?

Although the medical and consumer conceptions of recovery are virtually orthogonal in their origins, content, and ramifications, both views permeate the literature, causing well-documented confusion about the meaning of recovery [1–5]. Some conflation in the use of the term also results from articles which appear to cite the results of longitudinal outcome studies in support of their discussions on the consumer view of recovery [6]; and articles discussing recovery from a medical/scientific perspective, which appear to cite the role of political forces such as the President's New Freedom Commission in the genesis of the medical model of recovery [7]. The current chapter attempts to avoid such conflation by discussing the medical and consumer models of recovery as separate perspectives supported by distinct evidences.

Part I: The Medical Model of Recovery

The medical definition views recovery as an end state and focuses on symptom relief, alleviation, remission, and return to premorbid levels of functioning [5, 8]. This definition is grounded in the symptomatic experience of schizophrenia and spectrum disorders and recovery is generally viewed as akin to becoming asymptomatic, subthreshold with regard to meeting diagnostic criteria, regaining prior levels of premorbid functioning, or becoming literarily cured [9].

Due to its emphasis on an "end state," and its origin in treatment outcome studies, the medical definition is also synonymous with the "outcome definition" of recovery [5]. This definition emanated from changing conceptions of schizophrenia from one of a chronic psychiatric condition marked by functional deterioration to one characterized by heterogeneous outcomes [10, 11]. So pessimistic was the traditional view of schizophrenia that occasions in which individuals experienced marked improvements in symptoms or regained functional status were viewed as indicative of false positive diagnosis [11, 12]. Over the years, however, studies have emerged that have rebutted this pessimistic view. These include both short and long-term studies pointing to individuals experiencing significant remission and improved functioning with or without treatment [10, 13–15]. Various short-term studies have demonstrated that over 70% of individuals receiving standard treatments for schizophrenia experience "significant remission" to "full or complete remission" within the first year of treatment [16–19]. Some individuals receiving comprehensive treatments including medication management and psychosocial interventions have also experienced improvements in psychosocial functioning [16]. Longitudinal studies of outcomes in schizophrenia have demonstrated that only a fraction of individuals demonstrate a deteriorating course. Conversely, about 20–65% demonstrate moderate to good outcomes (although periods of symptom remission and exacerbation are common), and about 20% return to premorbid levels of functioning [13]. Recent studies have continued to support the heterogeneity of functional outcomes with longitudinal studies producing positive outcomes of up to 91% in a review of studies [14] when "positive outcomes" is defined as symptomatic remission.

Predictors of positive outcomes in these studies include good premorbid intellectual functioning, education, female biological sex, early discharge or short hospital stay, and younger age. Better educated participants also tended to have better cognitive functioning, and education was also associated with better social and vocational functioning. Early discharges or shorter hospital stays was associated with better community adjustment and better overall global functioning. Female participants tended to have better social outcomes than male participants, whereas younger participants tended to have better cognitive functioning. The socio-cultural context of individuals appears to have an impact on the course of schizophrenia symptoms [15]. The specific socio-cultural variables associated with heterogeneous outcomes are currently unknown but have been speculated to involve greater acceptance and tolerance of mental illness, and better social support networks usually involving family and members of the community [20].

Some have observed that improvement or recovery rates suggested in most studies represent underestimates of the potential for recovery in schizophrenia spectrum disorders. It has been suggested that this is because many individuals who experience symptoms do not present in treatment settings [5, 10]. Evidence supporting this assertion is usually drawn from the disparities between prevalence rates identified in epidemiological studies and the number of people that actually present in treatment settings [21]. It may be that these individuals represent cases that did not require hospitalization because they experienced less severe forms of illness relative to those requiring hospitalization, or individuals who had developed abilities to cope with symptoms without need for clinical care. Including this group of patients in long-term outcome studies may increase the recovery rates obtained from these studies.

With regard to the notion of "cure," a number of authors have highlighted the problems with adopting such a standard for chronic conditions such as schizophrenia [5, 8, 9]. First, in schizophrenia, similar to other chronic medical conditions, the notion of recovery as cure may be untenable, given that a disease process may be persistent even when symptoms undergo significant remission. For example, given their episodic nature positive psychotic symptoms can undergo significant remission, yet underlying cognitive impairments tends to be more unrelenting in nature. Thus cognitive impairments limit the ability to fully regain premorbid functioning even with full resolution of positive symptoms [9]. Second, the concept of cure is difficult to operationalize in schizophrenia [5]. For example, many patients experience loss of functions (e.g., increased asociality) even before the first psychotic episode; consequently, determining return to premorbid functioning may be indeterminate for an adult patient. Some studies do suggest that a fraction of patients experience "full recovery," characterized by complete symptom remission and return to premorbid levels of social and occupational functioning [10]. However, it is unclear if this constitutes cure, given that outcome studies primarily focus on symptom remission and psychosocial functioning, while ignoring other domains of illness such as neurocognitive functioning.

In addressing symptom status, realistic medical notions of recovery generally focus on remission of symptoms or decreased severity of symptoms. For example, Andreason and colleagues [9] in their definition focused on decreased severity of symptoms rather than complete absence of core signs or symptoms of disorder. The symptoms are subthreshold, not enough to meet diagnostic criteria, and they are not severe enough to cause marked impairment. Liberman and colleagues' [3, 22] definition also focused on decreasing symptom severity, which they conceptualized to be indexed on a continuous scale such as the Brief Psychiatric Rating Scale (BPRS), the Schedule for Affective Disorders and Schizophrenia (SANS), or the Positive and Negative Syndrome Scale (PANSS). A number of outcome studies have established various remission criteria based on these measures. For example, Liberman et al. [23] defined remission based on a positive symptom item threshold score of ≤ 3 on the SANS; and Clinical Global Impression (CGI) severity scale score of ≤ 3. Additional criteria include a CGI global impression of change score of no more than 2; scores of ≤ 2 (mild) on all SANS negative symptom global items, and a "full

remission" categorization when there are no residual positive symptoms. Liberman et al. [3] established a threshold score of ≤ 4, indicating minimal to moderate severity for positive and negative symptom items on the BPRS. Yen et al. established remission criteria of a mean score of ≤ 2 on positive, negative, or general psychopathology subscales of the PANSS [24]. Some studies of early psychosis have established strict criteria for remission defined as "absence of symptoms" or "full remission" [23, 25]. It should be noted, however, that the cited studies also included symptom severity as an outcome variable.

With regard to psychosocial functioning, outcome studies have used various criteria including operational definitions and global assessment of functioning scales. One example is found in the Liberman et al. [3, 23] definition, which emphasizes evidence of social interactions with others outside of the individual's immediate family members and treatment providers (at least once a week). It also requires involvement in age and culturally appropriate educational or vocational activities (at least part-time), and activities of daily living including management of medications and financial responsibilities. Studies have also used global assessment scales such as the Global Assessment Scale (GAS) and Global Assessment of Functioning (GAF) Scale to indicate levels of psychosocial functioning [26, 27]. Harding et al.'s [26] seminal study of recovery outcome categorized good functional outcomes as GAS scores ≥ 61 and the Torgalsbøen and Rund [27] study defined GAF scores ≥ 65 as indicative of adequate psychosocial functioning. None of these definitions require a return to premorbid levels of functioning; rather, they underscore improvements in psychosocial functioning.

Given that psychotic disorders are episodic by nature, extended periods of symptom remission and normal functioning would be necessary operational criteria to suggest recovery. Thus, attaining recovery from schizophrenia requires that a sufficiently extended period of time has passed during which symptoms are maintained at subthreshold severity with substantial improvements in functional status. For example, Liberman and colleagues [3, 22, 23] suggest two continuous years of sustained remission and normal functioning as reasonable standard for defining recovery from schizophrenia, whereas others suggest shorter or longer period of recovery (e.g., a 5-year period in the Torgalsbøen and Rund [23] study, and a 1-year period in the Harrow and colleagues [7] study).

In summary, outcome definitions of recovery incorporate both symptom remission and adequate psychosocial functioning for a specified duration as criteria. Although some studies incorporate the criterion of "absence of symptoms," this is not required in most definitions of recovery. Definitions do require that there is evidence of "normal", "good", or "improved" psychosocial functioning in the domains of social relationships, vocational or educational involvement, and activities of daily living, as indicated by GAS or GAF scores greater than 60. It is likely that the variability in recovery criteria established in individual studies also contributes to differences in recovery rates.

Of course, the more heterogeneous and positive outcomes reported for individuals with schizophrenia may be very well attributable to recent advances in interventions for the disorder. The effect of treatment programs on course and

outcome is schizophrenia is well illustrated by the classic Vermont-Maine longitudinal studies [26, 28–30]. These series of studies suggested that Vermont participants had better long-term outcomes compared to Maine participants due to the Vermont hospital's comprehensive treatment program of medication management and a host of psychosocial interventions. In recent years, there have been advances in pharmacological treatments targeting various active symptoms, and psychotherapy modalities that have served as useful adjuncts to medication management in treating symptoms and reducing risk for relapse. Interventions have also included vocational rehabilitation and supported employment activities geared towards improving capacity to work, and assertive community treatment geared towards assisting individuals function in the community. Variable outcomes may also be a product of the divergent targets and mechanisms of actions of the widely varying treatments offered in the treatment of schizophrenia. Individuals also differ with regard to how readily community resources are available to them. The heterogeneity in points of intervention, availability, and types of interventions contributes to heterogeneous outcomes in schizophrenia spectrum disorders.

The medical notion of recovery is not without its limitations. The first is a seeming categorical conception of recovery, meaning that individuals are classified as either recovered or not. A demerit of a categorical approach is that meaningful improvements in symptoms and psychosocial functioning may be lost simply because they do not meet set criteria. In some cases, this could be due to not meeting the duration criteria, level of psychosocial functioning, or symptom severity, all of which are mostly based on consensus or convention that may not hold up if investigated empirically. Liberman and Kopelowicz [3] suggest a dimensional approach to defining recovery. This approach focuses not on classifying individuals as either meeting recovery criteria or not, but rather on "degrees or extent of recovery" (p. 736). Thus, continuous scores are assigned to each individual's domains or facets of recovery including remission and level of psychosocial functioning and composed into an overall recovery score. The domains of symptom remission and psychosocial functioning can conceivably subsume additional sub-domains or lower-order facets. As suggested by Liberman and colleagues, these can include variables from BPRS or the PANSS as sub-domains of the remission domain, and vocational, educational, recreational, social, and interpersonal functioning as sub-domains of psychosocial functioning.

In a similar vein, Calabrese and Corrigan [31] address the question of whether all of the outcome dimensions are crucial to an outcome-oriented definition of recovery. On the one hand, the frequent discordance between symptom remission and psychosocial functioning observable in many long-term outcome studies may suggest that both should figure into determining if recovery has occurred. Such an approach arguably produces a comprehensive view of recovery. On the other hand, end state psychosocial functioning may be more crucial to the concept of recovery than remitting symptoms. Some individuals experiencing symptoms may have developed adaptive coping strategies or simply learn to live and function adaptively within or despite the limitations of symptoms. In such cases, symptom remission

may be less crucial to the experience of recovery from schizophrenia spectrum symptoms.

Another limitation of the medical or outcome notion of recovery is its limited scope, focusing exclusively on an objective assessment of remission and psychosocial functioning. As Bellack [5] notes, it generally ignores the subjective rating of recovery domains, which may be sometimes discordant with clinician ratings. For example, an individual may score within clinical range of the BPRS or the PANSS, yet report that the subjective experience of "doing better" and express to the clinician a readiness to return to full-timework. It is also possible for an individual to score low on clinical measures, yet report distress related to residual symptoms, "trauma" of symptoms, or stigma related to mental illness. Also missing are ratings of overall quality of life and health status, and the experience of family members. A definition proposed by Nasrallah, and colleagues [32] incorporated additional outcome domains including long-term symptom management, medication side effects, social and interpersonal functioning within the family context, and long-term physical health and wellness. Based on their definition, recovery involves continued medication management, decreasing dependence on family members, while fostering independent daily living skills, increasing engagement in vocational and/or educational functioning, improving social functioning, and fostering health behaviors and overall wellness. All outcome definitions, however, are limited in that they neither subsume key elements of the experience of individuals with schizophrenia reflected in consumer definitions, nor incorporate them in outcome studies [5].

Part II: The Consumer Model of Recovery

Although the ideas of the consumer model of recovery have been expressed in the writings of former patients [1, 2], the earliest definition of recovery was offered by Anthony and colleagues [33, 34] who describe recovery as a process in which an individual, who has suffered the devastating effects of mental illness, experiences a change in deep cited beliefs, attitudes, feelings, and values that result in increased hopefulness, and living a meaningful life, despite the limitations imposed by mental illness. The New Freedom Commission [35], Jacobson and Curtis [36], and Davidson and colleagues [37] have all reiterated similar definitions all of which underscore hope, empowerment, improvements, increased self-awareness, and change in self-concept in the process of recovery.

The consumer definition of recovery did not originate from the scientific endeavor to improve symptom status or even to enhance psychosocial functional outcomes but from socio-political forces that objected to the traditional models of mental health care delivery. Consumers and consumer advocates have historically expressed dissatisfaction with the traditional mental healthcare system, which they perceived as fostering dependence, disability, despair, hopelessness, and stigma [5]. Thus, the 1980s witnessed an evolution of the concept of recovery from that of the

medical model to a person-focused conception that emphasizes self-determination, hopefulness, mastery, and positive expectations in the lives of individuals with severe mental illnesses. This view of recovery has been championed by consumers [1, 2] and advocates of mental health system transformation including organizations like the National Alliance for the Mentally Ill (NAMI) and the National Empowerment Center, and has begun to influence policies and practices in state mental health systems [36, 38]. For example, the Independent Living Movement [38], which was founded and ran by individuals with physical disabilities promoted the idea that individuals with physical disabilities can live full and meaningful lives, regardless of their physical impairments. Thus, individuals can be fully engaged in social, vocational, and educational activities even if they never regain particular biological functioning (e.g., sight or hearing). This idea strongly influenced the mental health recovery movement, which adopted the ideas that full and meaningful existence was possible despite the presence of clinical symptoms and functional impairment.

Perhaps the most influential political forces that advanced the consumer recovery movement were the U.S. Surgeon General's report [39] and the work of the U.S. President's New Freedom Commission [35, 40]. The Surgeon General's *Report on Mental Health* underscored not only the need to promote and dispense recovery-oriented care, but the need to include consumers and their family members in treatment planning and decision making. While not official legislation, the Surgeon General's report pressured policy makers, treatment programs, and treatment providers to offer more consumer-focused care. The New Freedom Commission was instructed by executive order to conduct a comprehensive evaluation of the state of mental health care in both the public and private sector and offer recommendations. The commission in a final report recommended a fundamental transformation of the mental health care delivery system in the United States. The commission specifically recommended that mental health systems focus on fostering education about mental health as crucial to overall health; increasing the involvement of consumers and their families in mental health care; eliminating disparities in the availability and quality of care; fostering early detection and intervention through screening, assessment, and appropriate referrals; linking innovative research with excellent mental health care; and fostering the use of technology to access mental health care information. Along with the Surgeon General's report, the commission's recommendations have been at the forefront of dramatic transformations in mental health care delivery in several states and the Veteran's Affairs health care system.

The most widely held definition of recovery was developed as a result of the activities of the Substance Abuse and Mental Health Services Administration (SAMHSA) [41] during the National Consensus Conference on Mental Health Recovery and Transformation. The conference was attended by 110 expert panelist including consumers, family members, clinicians, researchers, advocates and others, with the objective of defining recovery and highlighting guiding principles for recovery-oriented clinical practice. This definition, generally termed the SAMHSA definition, states that "Mental health recovery is a journey of healing and

transformation enabling a person with a mental disability to live a meaningful life in the community of his or her choice while striving to achieve full human potential or personhood." (p. 1). The SAMHSA definition was also accompanied by guiding principles highlighted during the conference as characterizing recovery-oriented care. These principles are also synonymous with the domains, dimensions, elements, or components of the recovery process and they include: self-direction, individualized and person-centered, empowerment, holistic, non-linear, strength-based, peer support, respect, responsibility, and hope. As principles of recovery-oriented care, they are to be fostered by providers; as elements of recovery, they are characteristics or attitudes of individuals in recovery.

SAMHSA Recovery Domains

1. *Self-Direction* – involves the consumer defining and making life goals and determining how to go about accomplishing those goals. Consumers are primarily responsible for their own course through recovery and recovery-oriented care fosters a sense of self-efficacy and independence. Systems must afford consumers opportunities to make choices, provide choices, and afford opportunities for success or failure.
2. *Individualized and Person-Centered* – underscores the idiosyncratic nature of the recovery process. Similar to self-direction, this domain involves consumers determining a recovery path germane to their own preferences, needs, experiences, and tailored to their individual strengths.
3. *Empowerment* – like self-direction above, empowerment involves consumers assuming control over their lives, making decisions that impact their future, influencing their immediate environment, assuming responsibilities, exercising their rights, and making choices to address their needs and aspirations.
4. *Holistic* – The recovery process incorporates all the facets of the consumer's life including community life, education, occupation, relationships, social network, spirituality, community resources somatic, and mental healthcare, all of which play a role in the consumer's welfare. The consumer's self-concept is not one of "a person with mental illness" but a multi-faceted individual and recovery-oriented care fosters this self-concept by providing opportunities to engage in other social roles.
5. *Non-linear* – The consumer's recovery process does not occur in a predictable linear fashion but may be characterized by occasional setbacks (i.e., good days and bad days). The recovery process involves learning from setbacks and positive experiences in order to foster continued recovery.
6. *Strength-Based* – The recovery process focuses on harnessing the individual's qualities, abilities, aptitudes, and coping skills to addressing needs, aspirations, and social roles.
7. *Peer Support* – The recovery process involves interdependence on a support system. Fellow consumers play an important role for the individual in recovery

as role models, sources of useful experiential information, encouragement, and social support.

8. *Respect* – Respect for consumers includes the protection of their rights, elimination of discrimination and stigma in attitudes towards consumers, use of non-discriminatory and non-stigmatizing language, and acceptance of consumers by health care providers and the greater community.
9. *Responsibility* – Consumers are actively involved in fostering their own recovery including taking responsibility for their own self-care, learning and implementing their own coping strategies to promote wellness, understanding and interpreting their own mental health experiences.
10. *Hope* – An essential element of the recovery process and perhaps its driving force is a consumer's deep cited belief in their ability to overcome their illness, setbacks, and other obstacles that confront them as they strive to accomplish their goals.

A number of points are worth highlighting from these definitions: First, mental illness is only one aspect of an otherwise whole person with dreams, ambitions, personal attributes, values, hobbies, interests etc. Recovery involves embracing and engaging these other aspects of the self regardless of the status of symptoms. Recovery also involves overcoming the effects of being "a mental patient" – including discrimination, stigma, self-stigma, isolation, loss of valued social roles and identity, loss of sense of self and purpose in life, illness burden and iatrogenic effects of involuntary treatment and hospitalization-in order to retain or resume some degree of control over life. This process of resuming control is tied in with increasing self-efficacy and it may involve setting life goals, taking inventory of and engaging in interests, hobbies, ambitions, social roles, and responsibilities [37]. The consumer view also underscores the role of a social network that serves as a source of support. These may include family members, friends, peer support, fellow parishioners, treatment team, and other sources. Recovery may also involve symptom management although symptom remission is not central to this view of recovery.

The principles of the consumer model of recovery transcend diagnostic boundaries and apply well to both schizophrenia itself and schizophrenia spectrum disorders where isolation and loss of sense of self pervade. Within the context of schizophrenia and spectrum disorders, this consumer conception of recovery deemphasizes the role of symptom remission, "end state," or outcome functioning, rather underscoring the non-linear nature of recovery and overall functioning. This recovery approach is rooted in personal attributes and abilities of individuals who live with mental illness, thereby reframing the process of care around the individual's long-term expectations and lifetime aspirations. Recovery at its core is about finding purpose, meaning, and hope in the face of adversity. Finding one's way in dealing with the challenges of mental illness. Therefore, recovery-oriented practice emphasizes self-determination, self-reliance and identification of one's strengths, peer support and advocacy, and hope.

Qualitative Studies of the Consumer Conception of Recovery

Systematic investigations focused on aspects of the consumer notion of recovery such as the efficacy of recovery-based treatments are currently in infancy. In reviewing studies focused on the consumer notion of recovery, it is important to note that the research questions have a different focus besides symptomatic states or outcomes. Whereas studies of the medical definition of recovery have yielded clear recovery and/or improvement rates, investigations into the consumer view of recovery have focused rather on descriptions of recovery processes, pathways, and experiences. As such, no attempts have been made to quantify consumer-defined recovery rates [1]. Seeking such data may in fact be counter-intuitive to this idea of recovery given that individuals are not adjudged as recovered or not. The studies reviewed in this section provide evidence of the experience of having meaning or purpose despite illness and the commonality of pathways or trajectories to achieving this state.

The earliest evidence provided in support of this view of recovery came from autobiographical accounts and published testimonials of consumers rather than systematic studies or clinical trials [1, 2]. Personal stories and anecdotal evidence have been key in highlighting the personal experiences of patients dealing with symptoms and negotiating the mental health care system. Moreover, these personal accounts have raised awareness about certain dimensions of the recovery process such as the importance of hope, empowerment, self-management, advocacy, and mutual support; potential impediments and facilitators of recovery; and coping mechanisms that have been helpful in recovery. These personal accounts have been supported by a few qualitative studies, which are adaptable to studying person accounts and experiences, their meaning, and the impact of both the context of the experience and the interview [42]. For example, Davidson and Strauss [43] examined the role of renewing and rediscovering a coherent sense of self in the recovery process using a qualitative design. They conducted semi-structured interviews with 66 individuals who had participated in the Yale Longitudinal Study of Prolonged Psychiatric Disorder. The majority of the individuals included in the study had been diagnosed with either schizophrenia or schizoaffective disorder but others were diagnosed with a major affective disorder. Participants provided information about shelter, vocational and social functioning, symptoms, and coping strategies for a 2–3 year follow-up period and information obtained was interpreted for commonalities. Davidson and Strauss determined that individuals' rediscovery of a functional sense of self occurred in a developmental fashion. It begins with individuals realizing and embracing their potential or capacities despite mental illness. This is followed by a phase during which individuals take inventory and come to terms with their strengths and weakness. In the next phase, individuals begin to engage in activities that serve as confirmation or refutation of their perceived capacities. They integrate the results of these real-world experiments into their sense of self. The final phase involves harnessing the integrated sense of self as a buffer from mental illness, stressors, discrimination, stigma, and other negative social factors.

Spaniol and colleagues [44] used a qualitative design to provide evidence to support the notion that there are common pathways or trajectories to achieving a sense of recovery. The participants in their study were twelve individuals diagnosed with schizophrenia and schizoaffective disorder. These individuals had recently participated in a larger study examining vocational outcomes in several individuals diagnosed with a variety of mental illnesses. Spaniol and colleagues were interested in studying the aspects of recovery-orientation including contributing life events and experiences. They were also interested in identifying factors associated with the recovery process including barriers and contributors to recovery. Participants completed follow-up interviews for a period of 4 years in four to 8-month intervals. The hour-long interviews were open-ended, focused on eliciting information about current experiences, living and financial situation, relationships, status of symptoms, and life goals. In their qualitative analysis of the experiences of participants, the researchers identified three phases of recovery for participants. Similar to Davidson and Strauss' model [43], the process begins with a period of feeling overwhelmed by the experience of mental illness. During this period, participants had difficulty integrating their experiences and controlling their lives. This is followed by a period during which individuals begin to engage in interpreting their experience of psychiatric symptoms. This second stage ends when they begin to integrate this into other aspects of their lives. Although individuals in this phase tend to interpret their experiences using clinical explanations, they begin to identify coping strategies for dealing with symptoms. They also begin to develop confidence and independence in managing illness and other facets of their lives. In the final phase the individuals come to terms with the disability and fully integrated the disability into their overall experience. In this phase, they have also developed a stronger sense of self and belongingness, and are engaged in meaningful activities and role functions.

Although none of their participants reached the final role by the end of the 4-year follow-up, Spaniol and colleagues [44] suggested that a fourth phase during which individuals live beyond the disability of mental illness would be reached by individuals in the recovery process. In this phase, individuals live a full and meaningful life as mental illness becomes a very minute aspect of their existence, consistent with the consumer definition of recovery. Their study identified comorbid substance use problems, social disadvantage (e.g., low socio-economic status and its interaction with African American ethnicity), and earlier onset of symptoms as challenges to the recovery process. Individuals who progressed in their recovery cited having a support system such as friends, family members, fellow parishioners, effective medications, treatment teams, deity and spirituality as helpful in their recovery. Individuals tended to see themselves as being molded by their experience with mental illness. They viewed the process of regaining control over their lives as non-linear and sometimes interspersed with periods of instability.

Andresen, Oades, and Caputi [45] conducted qualitative analyses of consumer accounts and testimonials of their experience of recovery with the aim of integrating these consumer views into a coherent definition of recovery. They were interested in identifying coherent themes in consumer accounts, delineating the process of recovery, and identifying the stages of recovery. They retrieved journal articles

detailing first-person recovery experiences, from which they focused their analysis on 28 experiential accounts, 14 consumer-authored articles on recovery, eight qualitative studies of recovery. Their review revealed that consumer accounts often underscored four elements of recovery including hope, regaining a sense of self or identity, finding meaning or purpose, and assuming responsibility for recovery. They also integrated consumer views and the results of other qualitative studies into a five-stage model of recovery. They suggested that the recovery process begins with *moratorium*, during which the individual is confused and overwhelmed by illness and hopeless about the prospects of recovering. This is followed by an *awareness* stage, during which the individual realizes the possibility of recovery, perhaps through education, interaction with former patients, or a recovery-oriented clinician. The third stage is *preparation*, during which the individual reconnects with the self by taking inventory of strengths, weakness, hobbies, interests, aspirations, and values. In this stage, the individual also learns about symptoms and possible interventions; sets recovery objectives such as vocational and social roles; and readies to engage in recovery objectives. This is followed by a *rebuilding* stage, during which the individual begins to address recovery objectives including goals and responsibilities, symptom management, and addressing personal needs. The final stage is *growth*, during which the individual is fully engaged in recovery. The individual lives a full and meaningful life despite the disability, and has a positive view of self and the future. This stage may also involve continued symptom management and overall wellness.

Onken and colleagues [46] conducted a cross-sectional study of the perspective of consumers about factors that facilitate or impede their recovery process. The participants in the study were 115 individuals diagnosed with various psychiatric disorders, including 61% of the participants who had a diagnosis of severe mental illness and 36% diagnosed with a depressive disorder. They participated in 10 focus groups completed in nine states, each focus group comprising between 8 and 17 participants. Focus group members responded to questions assessing their perspectives on factors that have facilitated or impeded their recovery in five recovery domains including resources/basic needs, choices/self-determination, independence/sovereignty, interdependence/connectiveness, and hope. Group members also discussed their experiences in mental health services and evaluated whether these have been help or obstacles. Onken and colleagues' qualitative analysis revealed many themes. Participants often cited financial stability, transportation, communication services (e.g., phone connection), stable housing, privacy, and social networking as germane to meeting basic needs. The experience of the self as a whole person was fostered when participants had positive attitudes and beliefs about themselves, engaged in self-care and self-management, and took personal responsibility for their lives. The development of a coherent self was also fostered when participants advocated for themselves and educated themselves about illnesses. Participants highlighted the helpfulness of discovering their own strengths and talents, gaining knowledge and education, setting life goals, spirituality, making meaningful contributions, having an interdependent relationship with others, and personal dignity in their experience of hope and independence. They also viewed

system level variables such as the knowledge and availability of their treatment team, patient and family education programs, case management, continuity, cultural sensitivity, and system-client collaboration in treatment planning and staff training as associated with their sense of recovery.

A full review of all qualitative studies conducted to date is beyond the scope of the chapter. However, these and other studies have underscored aspects of the recovery process including the role of a support system, integrating illness in a multifaceted existence, symptom management, coping strategies, engaging in mastery and pleasurable activities, increasing hopefulness, independence, responsibility, and surmounting stigma [37]. It is unclear if the principles of recovery from the consumer perspective are universally applicable to all patients, given the heterogeneity of symptomatic experiences, idiographic factors (e.g., cognitive functioning and premorbid status), and contextual elements [5]. The qualitative data does, however, point to some core aspects of the subjective experience of having purpose and meaning despite illness that could be a start point in the journey of recovery.

Part III: Integrating Medical and Consumer Models of Recovery

Some authors have favored combining both views of recovery into one overarching definition having outcome and process elements [3, 47–50]. These authors have argued that rather than view the medical and the consumer conceptions of recovery as conflicting ideas on recovery, both perspectives should be seen as interrelated aspects of recovery. Their definitions also underscore the complexity of the phenomena underscored in consumer definitions of recovery. Hope and empowerment has underscored in the consumer model can also be viewed as subjective outcomes. Taking responsibility is a process that helps to achieve positive subjective states. Getting on with life is a subjective outcome that entails a sense that one is engaged in a life of meaning and purpose.

Liberman and Kopelowicz [3, 47] described the elements of the consumer definition of recovery as "subjective attributes" that are imperative in fostering positive recovery outcomes. Liberman and Kopelowicz comment that these subjective attributes, which themselves can be impacted by the therapeutic and environmental milieu of consumers, may in fact transmit the relationship between interventions and clinical outcomes including symptom remission and functional status. Similarly, the process elements of recovery may also be influenced positively by sustained positive outcomes. For example, an individual may feel increasingly empowered by being able to successfully implement skills learned in a therapeutic context in stressful situations. One concern that may be raised with Liberman and Kopelowicz's integration of both perspectives is that it appears to give primacy to the medical/outcome focused definition, while viewing the consumer elements as internal variables that may foster recovery outcome.

Noordsy and colleagues [48] presented a definition of recovery that subsumes outcome elements under consumer recovery principles. Their definition underscores three components or criteria for recovery including hope, taking personal

responsibility, and getting on with life. These three criteria reflect internal processes that are directly linked to measurable external and behavioral outcomes. Hopefulness as indexed on a self-report measure may be associated with behaviors such as verbalizing life plans and goals and engaging in activities related to their spirituality. Taking personal responsibility may be associated with behaviors such as active involvement in treatment planning, treatment adherence, and active learning and implementing of coping techniques. It also involves maintaining a healthy lifestyle which is also linked to improved symptoms and functional status. The third criteria of getting on with life not only involves a rediscovery of an active self outside of illness, but also subsumes various functional domains including involvement in recreational and meaningful activities, social relationships, and occupational roles. Thus, in this recovery model, elements of recovery outcomes are incorporated within the consumer definition of recovery.

Torgalsbøen [49] suggested a definition of recovery that avoids pitting the two perspectives against one another but rather ascribes equal weight of importance to outcome and process elements. Torgalsbøen's definition acknowledges both the subjective elements of recovery that individuals experience, as well as the objective indicators of recovery that practitioners, family members, and other members of the support system may perceive and adjudge as indicative of change. Both aspects of recovery are important with the subjective elements fueling the course of the symptom and functional status. Torgalsbøen suggested that operational definitions of recovery in outcome studies include elements of the subjective experience (e.g., hope, self-esteem) in establishing criteria for recovery, so that recovery *process* is also viewed as an *outcome*.

There are identifiable advantages to more integrative views of recovery. Integrative views of recovery may foster a line of research that allows the relationship between elements of the consumer-defined recovery and the medical conception to be studied systematically. Although both views of recovery are orthogonal in their origins, integrative views of recovery suggest that their elements are related. For example, as suggested by Liberman and Kopelowicz [47], increased hopefulness may be associated with increased motivation to engage actively in the treatment process. It may be that certain elements of the consumer view of recovery are associated with outcome in meaningful ways that may be of interest to consumers, practitioners, and researchers. Systematic investigations of the consumer view are currently limited. Thus, such a line of research would also allow the domains of recovery to be studied rigorously, including their association with other individual variables, changes in process elements over time, and their association with outcomes. Integrative views allow both perspectives on recovery to consolidate their relative strengths and weaknesses. Whereas the medical conception of recovery has been subjected to more systematic investigations through long-term outcome studies and short-term clinical trials, they have generally not assessed patient perspectives or taking inventory of their experiences. The consumer view has the advantage of being sensitive to the experience of patients, but is lacking in systematic studies or empirical data. An integrative view may foster the application of research designs that include both quantitative and qualitative methods of data

acquisition in outcome studies; thus allowing quantitative data to be collected and subjective experiences to be coded.

Part IV: Implications of the Consumer Model of Recovery for Practice, Education, and Research

Implications for Practice

Although both the medical and consumer views represent influential views of recovery; in recent years, the consumer view of recovery has been the "recovery model" permeating services and treatment settings. Calls from consumers, advocates, family members, and political forces have led to systemic changes in many countries including the United Stated, United Kingdom, Canada, Australia, Ireland, and New Zealand. In addition, some mental health professionals have called for establishing the consumer view of recovery as an overarching framework for dispensing treatment services [51, 52]. This implies that treatments and interventions for schizophrenia and spectrum disorders should be geared towards fostering the consumer sense of recovery. This would conceivably influence the types of interventions that are developed, the strategies for disseminating such interventions, and how the effectiveness of such interventions is evaluated. Anthony [51] suggested that recovery-oriented systems would offer nine vital services to consumers including treatment for symptoms, crises intervention, case management, rehabilitation, enrichment, rights protection, basic support, self-help, and wellness/prevention services. These services directly target various crucial areas besides symptom relief including physical health status, opportunities to engage in roles, empowerment, personal growth, access to services, safety, and basic needs. Guided by the principles of the consumer model of recovery, interventions would ideally foster an overall sense of well-being, hopefulness, independence, and other elements of recovery as discussed in previous sections.

The recovery model has fueled efforts by mental health systems to include as part of their periodic services assessments, consumer-centered variables assessing internal states and community functioning rather than just symptom status. In the United States, many state mental health systems have adopted recovery definitions as visions or mission statements to demonstrate their commitment to recovery-oriented care, although the overall grasp of systems about recovery differ [36]. The recovery model has also been the driving force behind the development of consumer-ran programs, mutual-help groups, and the Certified Peer Support specialist programs, all of which currently serve as useful additions to treatments received in traditional treatment settings. They offer opportunities learning and implementing problem-solving and coping strategies, assist in fostering hope and empowerment, providing information, help in accessing community resources, they provide social support, and are potential models of recovery.

The consumer model of recovery also has an impact on the process of treatment planning. It suggests that consumers and family members should be more

involved in treatment planning, which should be centered on the patient's goals and objectives, and the decision-making process about the types, dosage, frequency, and termination of interventions they receive. Treatment objectives should neither focus primarily nor exclusively on symptom management but on engagement in roles, social relationships, hobbies, educational interests, occupation, spirituality, and other life dimensions that the consumer is interested in pursuing. Another implication of the consumer model of recovery is the development and dissemination of self-help forms of interventions [53]. This is linked to the principles of empowerment, independence, and responsibility as characterizing recovery-oriented care. Self-help intervention programs such as the Wellness Recovery Action Plan (WRAP) [54] allow consumers to take inventory of their own strategies and techniques for managing their symptoms, and implement them as needed.

A practice-related challenge is how recovery-oriented services will be delivered and funded in mental health systems. Many systems are currently incorporating peer support specialists into their treatment teams, thereby putting former patients in positions to be partners in health care delivery. However, peer support specialists often face many challenges in their role including poorly defined responsibilities, power struggles with other members of the treatment team, limited supervision, and limited resources to help other consumers [55]. The range of services offered by peer support specialists may become broad in some settings that it causes other providers (e.g., case managers) to be eliminated. Compensation for the services of peer support specialists is another challenge to systems transformation. Some settings may be reluctant to employ support specialists because of concerns about third-party reimbursement for their services. Overall, systems are faced with the challenge of integrating recovery-based care with other services in a way that is feasible.

Implications for Education

While the consumer model of recovery is making its way into systems of care, it has wielded less influence in academic, training, and research settings where the medical model of recovery remains influential. In a recent survey of the perception of psychiatry and psychology residents about the meaning of recovery, Buckley and colleagues [56] determined that most residents offered definitions consistent with a medical model. Following introduction to principles of the consumer view of recovery, residents considered these ideas "new" and also expressed concerns about being able to address recovery principles within the constraints of a brief session. For prospective practitioners, limited exposure to the consumer model of recovery during their training may put them at a disadvantage when they begin to practice in clinical settings that have adopted this model. Thus, an implication of the ongoing systems transformation in clinical settings is the need to foster readiness among prospective mental health professionals in recovery-oriented practice. An example of this effort is the Georgia Recovery-based Educational Approach to Treatment (Project GREAT) [57], an educational program developed in the Department of Psychiatry and Health Behavior at the Medical College of Georgia with the goal

of disseminating recovery principles and training practitioners in recovery-based interactions. An evaluation of the Project GREAT program educational curriculum indicated that doctoral level practitioners (psychiatrists and psychologists) and psychiatry and psychology residents who participated in a workshop based on the curriculum increased their knowledge of recovery following the educational intervention on a variety of measures. When compared to practitioners in another academic department not exposed to the curriculum, they demonstrated higher knowledge and recovery-promoting attitudes than the comparison group. This study supports the efficacy of Project GREAT at increasing knowledge of recovery and fostering recovery-promoting attitudes. It also suggests that educational programs may be crucial in the ongoing recovery-based systems transformation through the dissemination of information about recovery and recovery-based practices.

Implications for Research

Translating the consumer model of recovery to patient care requires that it be measurable so that it is conceivable as part of periodic assessments completed during patient care. A measurable construct is also important in scientific endeavor, allowing recovery to be studied in relation to other variables relevant to the study of schizophrenia spectrum disorders. Assessment begins with a clear operational definition of recovery and the development of a system of measurement drawing from self-report, clinical rating, and/or objective measurement modalities (e.g., cognitive tasks). Whereas measures of the medical conception of recovery have been well-established, assessment of the consumer-view of recovery is in relative infancy [58, 59] although a number of measures have been developed recently. Further psychometric work of the recovery construct is warranted including additional reliability and validity studies of recently developed instruments, and further elucidation of the latent structure of the recovery construct. Whereas qualitative studies have suggested that recovery progresses through stages, this has yet to be systematically investigated with quantitative and longitudinal research designs.

A challenge for research is how to best understand the consumer recovery construct, which evolved out of the experience of consumers but is currently limited in empirical support. Many of the elements of recovery highlighted in definitions (e.g., SAMSHA domains) strongly overlap and in some cases appear redundant. There needs to be clarity about how elements of recovery relate to each other and the recovery construct through latent variable modeling (e.g., factor analyses) and other statistical models. According to Cronbach and Meehl [60], the process of construct validation involves establishing a nomological network of a construct that represents a set of laws about its pattern of relationships with other constructs. There is currently a dearth of studies that have investigated how the consumer view of recovery relates to other meaningful constructs including community functioning, quality of life, overall well-being, internalized stigma, discrimination, etc.

Traditionally, treatment outcome studies have evaluated interventions based on their capacity to foster symptom remission and improved functioning. The consumer

model of recovery dictates that treatments should be evaluated on their ability to foster both the process and subjective experience of recovery. Some authors have argued that current empirically supported treatments for schizophrenia can be consistent with the recovery model when they are tailored to consumer needs, foster feelings of mastery, and encourage a sense of partnership between consumers and providers [5]. On the other hand, Frese and colleagues [61] observed that recovery and evidence-based practices are often viewed as alternatives by consumers, and whereas more severely disabled individuals may benefit from evidence-based practices, consumers who have experienced significant improvements may gravitate towards the recovery model. The consumer view of recovery has not been extensively evaluated in the context of clinical trials to determine its association with clinical outcomes. This line of research may also inform about what treatment interventions, processes, and non-specific factors are associated with consumer-defined elements of recovery.

Conclusions

Despite their distinct origins and focus, medical and consumer models of recovery offer a much more positive outlook on schizophrenia than the traditional Kraepelinian view. Although the line of research evidence bearing on both perspectives are quite different, evidence of positive longitudinal outcomes for many patients, and evidence of personal growth, self-discovery, and wellness despite illness, offer a beacon of hope for patients and their family members. The consumer model of recovery is wielding an influence in service systems in many clinical settings, representing an overarching framework for patient care. It encourages consumers and family members to collaborate with treatment teams in determining their care and focuses on the overall wellness of the consumer. Integrating both the medical and consumer models of recovery has distinctive value for individuals with schizophrenia including allowing both perspectives to consolidate each others strengths and weaknesses. Immersing the consumer-defined construct of recovery in systematic clinical studies would increase our knowledge about the recovery construct in schizophrenia and spectrum disorders. The manner in which the two conceptions of recovery relate has enormous potential for adding to our understanding of the nature and treatment of schizophrenia.

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Chapter 2
The Magic Shotgun: Does It Fit the Clinician and Will It Point at Schizophrenia?

Ann M. Mortimer

Abstract Numerous lines of evidence converge to suggest that while dopamine-2 receptor antagonism may be necessary for effective schizophrenia treatment, it is as yet insufficient. Network theory indicates that a number of subtle alterations to biological systems are required to change their output effectively: many candidates for such alteration have arisen through preclinical science. Glutamate modulation is currently very popular but as yet unproven: serotonergic and cholinergic mechanisms are also being utilised in putative antipsychotic development. Most pipeline antipsychotic drugs have an affinity profile distributed across a number of therapeutic targets. In practice the majority of patients are treated with more than monotherapy, but the effectiveness of such regimes is not particularly impressive, certainly in groups of patients: monotherapy continues to be recommended. However, there is an increasing volume of augmentation trials which indicate that additional medications from numerous pharmacological classes may be of assistance in the individual patient if not the group. It is very important to specify and target the residual problematic symptoms when attempting rational polypharmacy, and an exit strategy is essential. The only existing magic shotgun is clozapine which, despite its many drawbacks, continues as the sole effective therapeutic option in treatment resistant illness. New techniques of drug discovery including individual affinity and gene based strategies hold much promise in the design of future antipsychotic drugs. It seems highly unlikely that there will be a magic bullet for schizophrenia: it is to be hoped that some of the magic shotguns in development, both polypharmacy strategies and new antipsychotic drugs, will reach their target eventually.

Keywords Schizophrenia · Magic Shotgun · Polypharmacy · Monotherapy · Dopamine · Glutamate · Serotonin · Drug Discovery · Antipsychotic

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Abbreviations

NMDA	N-methyl-D-aspartic acid
HT	serotonin
D	dopamine
GABA	gamma amino butyric acid
EPS	extrapyramidal side effects
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
RCT	randomized controlled trial
M	muscarinic
DMXBA	3-(2,4-dimethoxybenzylidene)-anabaseine
CB	cannabinoid
cAMP	cyclic adenosine monophosphate
PANSS	Positive and Negative Symptoms in Schizophrenia Scale
NSAIDs	non-steroidal anti-inflammatory drugs
H	histamine
MAOI-B	monoamine oxidase B

Introduction

The pathophysiology of schizophrenia remains, essentially, unknown. The discovery that dopamine receptor antagonism had an antipsychotic effect led to the dopamine hypothesis of schizophrenia, resulting in understandable hope that drugs which downgraded dopaminergic neurotransmission would prove a "magic bullet" to treat the disorder. The concept of the magic bullet, a single drug for any specific disorder, has a long history in medicine. The term "magic bullet" was coined by the German scientist Paul Ehrlich, who introduced the arsenic based drug salvarsan for the treatment of syphilis in 1910. Unfortunately, biological systems are complex entities: Cernansky et al. [1], and a recent editorial [2] state that network theoretical approaches suggest that the most efficient means of modulating the output of a network is a number of adjustments of small to moderate degree, applied to different parts of the network, rather than severance of one connection within it. This complexity is reflected in the limitations of the dopaminergic treatment approach in schizophrenia: partial rather than complete response is the modal clinical outcome, and up to a fifth of patients are treatment resistant. The only drug effective in treatment resistance, clozapine, has multiple affinities and is not a strong dopamine antagonist. Howes and Kapur [3] show that functional neuroimaging suggests that dopamine anomalies are "downstream" of the prior pathophysiology. Moreover, despite the proliferation of official guidance most if not all of which insists upon antipsychotic monotherapy alone as the ideal in schizophrenia treatment, Taylor [4] points out that in real life practice this is unusual. Furthermore Lepping and Harbourne [5] suggest that the "monotherapy = good, polypharmacy = bad" mantra may be challenged.

Monotherapeutic imprecations do not generalise to other common chronic diseases, many of which such as cardiac disease and diabetes are rarely managed with a magic bullet but with combinations of therapies designed to treat multiple aspects of pathology. Indeed, Hayhurst et al. [6] found that patients prescribed more than one antipsychotic drug are more severely ill and more compliant with treatment, consistent with the need for if not the utility of this approach. Even in disorders such as epilepsy where single drugs may be utilised as monotherapy, Bianchi et al. [7] state that they modulate multiple ion channel targets. These considerations are compatible with a "magic shotgun" treatment analogy in schizophrenia [8]. On the other hand, after 50 years of research and drug development, dopamine antagonism remains the *sine qua non* of antipsychotic action: no drug lacking this action has ever been reliably shown to possess clinical usefulness in schizophrenia. Moreover, the only drugs which reliably induce psychosis in healthy volunteers are dopaminergic, classically amphetamine. Glutamatergic (NMDA receptor) antagonism may result in psychotogenic effects, but these seem less convincing than generally assumed [9]. Furthermore, glutamatergic strategies have overall been disappointing in antipsychotic treatment. Mortimer [10] states that such unpromising realities sit in the context of relatively poor evidence for the use of combination and augmentation strategies, alongside concerns about non-compliance, side effects and interactions. For instance, a small open study of 53 patients examined the effects of tapering and stopping antidepressant and mood stabilizing medications in patients with stable chronic schizophrenia so that they were maintained on antipsychotic monotherapy alone. Only four patients worsened during a follow-up period of up to 18 months: the additional effectiveness of polypharmacy was very limited if the patient was established on adequate monotherapy [11]. As a whole, such issues continue to inform monotherapeutic imprecations.

This chapter will examine the evidence for the viability of the magic shotgun approach in schizophrenia. "More than monotherapy" comprises several strands: alternatives to dopaminergic mechanisms of antipsychotic action, how these are being developed as "pipeline" antipsychotic drugs, strategies to manage nonremitting symptoms, and ways of addressing the schizophrenic penumbra of affective symptoms, cognitive impairment, compromise of personal and social function, behaviour disorder and substance abuse.

Taking the Analogy Further

Bullets are fired by rifles, one at a time. The target, inanimate or otherwise, should be visible, slow moving or stationary. Therefore the rifle is aimed at the target before pulling the trigger. Shotguns by contrast are loaded with cartridges containing several hundred tiny metal balls (shot): these disperse as their distance from the muzzles of the gun increases. The analogy with schizophrenia is that instead of relying on a single bullet, many particles of shot i.e. multiple potential mechanisms of action afford a better chance that some of them will hit the target: they are spread across a much greater area than a single bullet.

The properties of shotgun cartridge loads make shotguns ideal for shooting at small targets which appear suddenly and move rapidly, such as clay pigeons and game birds. There is no time to aim a shotgun, therefore the gun is said to be "pointed". The trigger is pulled when the gun is pointing where the shooter thinks the target is going to be by the time the shot has travelled from the muzzle of the shotgun to the anticipated position of the target. This is an apt analogy in schizophrenia: our therapeutic armamentarium is pointed at where we think the pathophysiology takes place, but this necessarily relies upon currently unproven assumptions.

Furthermore, unlike a rifle the shotgun must "fit" the shooter when mounted to the shoulder and swung along the predicted trajectory of the target. If the gun is too long, short, narrow or deep, or if unadjusted for eye dominance, the gun is not pointing where the shooter thinks it is. Again, this is an apt analogy in schizophrenia. For instance although clozapine has numerous affinities including dopamine antagonism, none has been associated with its superior efficacy: we do not know where it is pointing, yet.

Mechanisms of Action and "Pipeline" Antipsychotic Drugs

Dopamine Receptors

Most putative dopaminergic antipsychotic drugs possess more than D2 antagonism: indeed all atypical drugs apart from amisulpride also antagonise 5HT2 receptors, an action thought to be responsible for less extrapyramidal side effects. Of the five varieties of dopamine receptor, it is known that D1 and D5 antagonism is not antipsychotic, D3 and D3 antagonism is definitely antipsychotic, while D4 antagonism may downgrade glutamatergic activity. Partial agonism of D2 receptors as in the case of aripiprazole represents a further variation. It has been suggested that aripiprazole may act through an alternative mechanism, functional selectivity. This proposes that although aripiprazole acts through a single receptor, the D2 receptor, its signalling effects differ markedly according to the neural pathway where the receptor occurs. Thus a drug could act as an antagonist along one pathway, and as an agonist elsewhere [12]. This would confer a bewildering variety of actions upon an apparently simple drug.

There are a number of "pipeline" drugs which combine antagonism or partial agonism of dopamine receptors with or without actions upon various serotonin receptors. For instance Kiss et al. [13] state that cariprazine, a dopamine D3 receptor-preferring, D3/D2 dopamine receptor antagonist-partial agonist, is an antipsychotic candidate. Some drugs also block calcium channels, which may prevent excess glutamatergic activity, while others seem intrinsically active in glutamatergic models of psychosis as well as the dopaminergic variety. For instance, bi-acetylated l-stepholidine (l-SPD-A), a novel dopamine and serotonin receptor dual ligand, possesses such activity [14]. Another idea is to combine conventional

antipsychotic drugs with GABA in ester form, potentially to reduce EPS and offset excess glutamatergic activity: Appel et al. [15] and Fitzgerald [16] state that BL-1020 is a novel antipsychotic candidate with GABA-enhancing effects. As yet there is no evidence that these drugs will be more efficacious than current options. Indeed aripiprazole despite its elegant and appealing theory of action is no more effective than any other antipsychotic drug, although undoubtedly better tolerated in many respects.

Glutamate Receptors

There is general agreement that a glutamate deficit is a likely contributor to pathophysiology in schizophrenia, with the NMDA receptor, its co-agonist the glycine site, the glycine transporter, the AMPA receptor and the metabotropic glutamate receptor particular foci of interest. Most if not all of these, furthermore, exist in different versions: as with dopamine receptors this indicates multiple potential therapeutic targets. The glutamate deficit is thought to lie in inhibitory control of glutamatergic neurotransmission, resulting in pathological neuronal excitability. The NMDA receptor overall inhibits glutamatergic neurotransmission: NMDA antagonists elicit schizophrenia-like symptoms in healthy volunteers and exacerbate the symptoms of patients, although Pomarol-Clotet et al. [17] state that there is some doubt about the extent of these effects and their relevance to schizophrenia psychopathology. Nevertheless, the glutamate and serotonin efflux which results from NMDA antagonism in animal models is prevented by clozapine, whereas haloperidol is only able to prevent glutamate efflux [18]. This suggests that both mechanisms are relevant in schizophrenia. Unfortunately, a number of studies employing glutamatergic agents have been less than successful overall. Drugs have usually been added to existing antipsychotic treatment, with small or variable results.

By contrast Patil et al. [19, 20] reported that LY2140023, an orally active prodrug of LY404039 which is an agonist at the metabotropic glutamate receptor, demonstrated antipsychotic action as monotherapy which was statistically equivalent to olanzapine in a 4 week trial. Nonetheless Harrison [21] argued that LY2140023's effects were less in every efficacy measure than those of olanzapine. A further trial announced in March 2009, via the Internet [22] states that the results failed to show separation of either LY2140023 or the active comparator, olanzapine, from placebo, owing to a placebo response double that usually observed. The drug remains in development even so, alongside similar pipeline drugs which act as dopamine partial agonists as well.

Metabotropic allosteric modulators are also in development: their effects may be more enduring than those of metabotropic agonists. Schlumberger et al. [23] note that some are active in dopaminergic animal models of psychosis as well as glutamatergic models. Similarly, glutamate AMPA receptors activate the NMDA receptor: AMPA agonists are also in development.

The presence of glycine is an absolute requirement for the activation of the NMDA receptor by glutamate. Glycine supplemention has very modest effects given its poor brain penetration, and thus it affords little clinical utility. Chiusaroli et al. [24] suggest that functional modulation of the site, however, is a plausible alternative. Heresco-Levy et al. [25] found that the NMDA co-agonist d-serine, supplementing risperidone or olanzapine, induced the >20% symptom reduction routinely used as a response criterion in one-third of patients in a crossover double-blind placebo RCT. Further work on glutamatergic augmentation strategies has, however, been disappointing. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST) was a 16-week double-blind, double-dummy, parallel group, randomized clinical trial of adjuvant glycine, D-cycloserine, or placebo in the treatment of negative symptoms and cognitive impairment: disappointingly, Buchanan et al. [26] concluded that that neither glycine nor D-cycloserine was generally effective for treating negative symptoms, or cognitive impairment.

Harsing et al. [27] propose that inhibition of the glycine transporter in order to increase synaptic availability of glycine is a further means by which to enhance its actions. Sarcosine, a weak selective inhibitor of the glycine transporter, and its analogues have similar drawbacks to glycine itself: Lane et al. [28] noted that results in one trial of sarcosine monotherapy were not encouraging. However potent selective glycine transporter inhibitors which are not sarcosine analogues seem more promising: these may afford cognitive remediation and potentially better tolerability than dopaminergic antipsychotic drugs [29]. Very interestingly, clozapine inhibits 30% of glycine transporter activity [30].

Other potential approaches include inhibition of D-amino acid oxidase, an enzyme which degrades D-serine. D-serine like glycine acts as an NMDA co-agonist. A polymorphism of the gene for this enzyme has been associated with schizophrenia in a number of ethnicities, and there is evidence of overexpression of the gene in post-mortem samples. Kinney and Sur [31] state that several D-amino acid oxidase inhibitors have been the subject of patent activity.

Finally, glutamate transporter proteins may prove a substrate for novel antipsychotic action. These are subsumed within the excitatory amino acid transporter group (EAATs). There are five subgroups: the third, EAAT3, appears to have a specialised function in respect of maintaining synaptic glutamate levels. Dunlop and Marquis [32] report that an inhibitor of EAAT3, NBI-59159, had antipsychotic activity in an animal model.

Muscarinic Receptors

Stone and Pilowsky [33] argue that there is some evidence of a muscarinic receptor deficit in schizophrenia, which could be associated with a “downstream” glutamatergic hypofunction. Unfortunately, most muscarinic agonists are not sufficiently specific for the M1 and M4 receptors thought to be involved: their peripheral actions at M2, 3 and 5 receptors confer dose-limiting toxicity. Conn et al. [34] point out that no muscarinic agonist has yet been launched although Vanover et al.

[35] note that preclinical work continues. Furthermore, Weiner et al. [36] state that N-desmethylclozapine, the major metabolite of clozapine, possesses powerful muscarinic agonist properties and is tolerable. This has led to suggestions that muscarinic agonism could be responsible for the superior efficacy of clozapine in treatment resistant illness. It is unlikely that N-desmethylclozapine is an effective antipsychotic drug on its own, as it is inconsistently active in animal models predictive of clinical antipsychotic activity. However, Lameh et al. [37] and Netesan et al. [38] indicate that it may have some adjunctive use. Even so, Deliliers et al. [39] conclude that in-vitro work suggests the risk of neutropenia would not be any less than with clozapine. Interestingly, N-desmethylclozapine is also a D2 and D3 partial agonist: its lack of efficacy in animal models is puzzling.

An alternative to direct agonism of specific muscarinic receptor subtypes is allosteric modulation. Leach et al. [40] mention that these mechanisms seem to vary more between subtypes: such drugs are currently in development.

There is some evidence that patients with schizophrenia are deficient in hippocampal alpha7 nicotinic receptors and that their ubiquitous heavy smoking is an attempt at self-medication by the provision of an exogenous ligand. Agonism of the receptor has been shown to enhance cognition: Freedman et al. [41] reported that a selective partial nicotinic agonist, DMXBA, did not deliver such effects but reduced negative symptoms.

Serotonin Receptors

Combination of a range of dopaminergic and serotonergic actions continues to represent a strong theme of drug discovery.

Watanabe [42] and Wadenberg [43] state that the antipsychotic drug bifeprunox appears to be very similar to aripiprazole, combining efficacy with very good tolerability on the basis of dopaminergic and serotonergic 5-HT1A partial agonism. Agonism or partial agonism of the 5-HT1A receptor serves to reduce the motor effects of dopamine antagonism, a similar effect to 5HT2 antagonism as in most atypical antipsychotic drugs. Moreover, McCreary et al. [44] note that 5HT1A agonism is thought to enhance antipsychotic effects on positive, negative and cognitive symptoms and also treat attentional, depressive and anxiety symptoms. Furthermore, Newman-Tancredi et al. [45] indicate that bifeprunox unlike aripiprazole has marked activity in rodent models of anxiety.

Mortimer [46] states that there are numerous putative antipsychotic drugs in development including most of the possible combinations of dopamine and serotonin receptor subtypes, utilising antagonism, partial agonism or both according to preclinical evidence.

Three serotonin receptors are of particular interest. Firstly, Wang et al. [47] report that inverse agonism of 5-HT2A receptors with the drug pimavanserin (ACP-103), which is devoid of dopaminergic activity, is active in animal models of psychosis. Snigdha et al. [48] found that it renders subtherapeutic doses of atypical

antipsychotic drugs effective in glutamatergic models of psychosis. Secondly, agonism of 5-HT2C receptors, originally studied in anxiety and depression, decreases dopaminergic neurotransmission without affecting the striatum, thus affording less potential for motor side effects. Marquis et al. [49] and Siuciak et al. [50] report that two agonists, WAY-163909 and CP-809.101display antipsychotic-like activity in animal models. Finally, 5-HT7 receptors are localised in the thalamus, which is important in sensory processing. Many atypical antipsychotic drugs act as antagonists at these receptors: clozapine is a strong inverse agonist. In animal models of psychosis using specific antagonists such as SB-269970, Galici et al. [51] note that there is some evidence of antipsychotic-like activity. Novel potential antipsychotic drugs which combine 5-HT7 antagonism with M4 agonism are being synthesised: Suckling et al. [52] found that one of them, "compound 29", was active in an animal model of psychosis without manifesting any in vitro dopaminergic affinity.

Other Potential Substrates for Antipsychotic Action

Birth injury and early infections are associated with increased risk for schizophrenia. Such insults may be associated with the production of pro-inflammatory cytokines. Indeed, Drzyzga et al. [53] state that antipsychotic drugs can act as anti-inflammatory agents. Muller and Schwarz [54] propose that excess cytokines promote central metabolism of tryptophan to kyenuric acid, the only known endogenous NMDA antagonist. Kyenuric acid is also a strong antagonist of the alpha 7 nicotinic acetylcholine receptor.

Selective cyclo-oxygenase-2 (COX-2) inhibiting anti-inflammatory drugs block the synthesis of prostaglandin E2 (PEG2), a potent inducer of cytokines, thus obviating these effects. Muller et al. [55] concluded that preliminary trials using the COX-2 inhibitor celecoxib as an adjunct to risperidone demonstrated beneficial effects on cognition and symptoms, but only during the initial few years of illness.

Dopamine agonism is known to upgrade the activity of histaminergic neurons. It would appear that the converse is also the case: Ligneau et al. [56] state that the potent H3 inverse agonist BF.649 functionally antagonises animal behavioural responses to dopamine agonists and NMDA antagonism.

Given converging evidence of cannabis abuse as a risk factor or contributory cause of schizophrenia, the cannabinoid CB1 receptor antagonist rimonabant was trialled recently, but without success. Nonetheless, Ballmaier et al. [57] suggest that CB1 antagonists mimic clozapine in certain animal models. Roser et al. [58] found that the drugs SR141716A and cannabidiol, both CB1 antagonists, demonstrate antipsychotic properties in volunteers and patients.

Organic selenium compounds exhibit a variety of biological activities. They are antioxidant, neuroprotective, anti-apoptotic and they inhibit glutamatergic excitotoxicity. Machado et al. [59] reported that an organic selenium compound, $(F_3CPhSe)_2$, was found active in an animal model of psychosis.

D2 receptor antagonism results in raised intracellular cAMP levels. This has led to the assumption that raising cAMP levels by other means, such as inhibition of the phosphodiesterase (PDE) enzymes which break it down, will produce antipsychotic effects. Siuciak et al. [60] demonstrated that rolipram, a specific PDE4 inhibitor, prevents cAMP degradation and had antipsychotic effects in animal models, although Kanes et al. [61] argued that only slightly larger doses induced motor effects. Halene et al. [62] note that other PDE4 inhibitors are under scrutiny. Siuciak et al. [63] and Menniti et al. [64] suggest that PDE10 is another enzyme whose inhibition has been examined in preclinical models of antipsychotic activity and side effects, with some promising results.

There is some evidence that neurosteroids are relevant to schizophrenia pathophysiology. Bortolato et al. [65] indicate that finasteride and other inhibitors of 5-alpha-reductase (5AR), a rate limiting enzyme in brain steroidogenesis, have antipsychotic-like effects in preclinical models.

The natural ligands of gastrin-releasing peptide receptors are the bombesins, small peptides originally isolated from frog skin. The receptors are expressed on neuronal membranes and appear to have a function in neuroendocrine regulation. Kauer-Sant'Anna et al. [66] report that an antagonist, RC-3095, is active in animal models of psychosis.

The drug iptakalim opens neuronal potassium adenosine triphosphate channels (KATP). It modulates dopaminergic and glutamatergic release in the forebrain: Sun et al. [67] propose that it is active in some animal models of psychosis.

Current Approximations to the Magic Shotgun: Are They Any Good?

Many randomised and often placebo controlled and double blind studies of polypharmacy have been published. Although evidentially superior to case reports and case series, the numbers in most of these studies are small, a few dozen or less. This is far fewer patients than would be needed for market authorisation licensing trials. Such low numbers no doubt reflect the lack of commercial interest in these studies, and therefore a paucity of funding to interested investigators. A more prosaic drawback attaching to most of these studies is that the reporting of the active treatment's superiority is in statistical rather than clinical terms. This makes the results difficult to interpret.

Consideration of in what way the patient is failing to get better is integral to any rational approach to polypharmacy. In the author's experience, persistent positive symptoms are the most common way in which treatment fails. Disruptive behaviour and dysfunctional personal interaction afford more obvious risk than negative symptoms and secondary compromise of personal and social function, which can be ameliorated by social care. Other inadequate responses may stem from cognitive impairment, again manifest in terms of poor personal and social function. In the

author's experience affective symptomatology tends to be less of a problem, whereas the escalating prevalence of substance abuse and noncompliance certainly is not.

Polypharmacy cannot lessen treatment failure if the patient is not taking their medication, or is antagonising it with self-prescribed substances. Similarly, affective issues "cover a multitude of sins" such as adjustment issues and understandable misery as well as depression secondary to substance and personality issues. Moreover, there is little point in attributing deficient personal and social function and intellectual compromise to schizophrenia if the patient functioned poorly before illness onset. It therefore behoves the clinician to think carefully about what it is they are trying to achieve and whether or not it is realistic to attempt to achieve it. Very few of these consequential matters have been explicitly considered within polypharmacy trials. Neuroscientific rationale, on the other hand, is emphasised in terms of potential explanatory mechanisms derived from preclinical science. Moreover there is a tendency to add other classes of psychotropic drugs to antipsychotic treatment simply because they have become available, without any molecular justification.

More than One Antipsychotic Drug

Paton et al. [68] state that a recent meta-analysis of clozapine combined with another antipsychotic drug concluded that the combination was worth trying on an individual patient basis. However, there are negative studies as well as positive ones: Freudenreich et al. [69] Akdede et al. [70] and Honer et al. [71] state that this is the case for combinations of clozapine with risperidone. Furthermore, Barbui et al. [72] note that meta-analytic reviews concluded that combining clozapine with another antipsychotic drug only worked in open studies, the advantages were absent when double blind studies were scrutinised. Cipriani et al. [73] and Honer et al. [74] conclude that overall the evidence was too poor to support specific recommendations.

Reviewing olanzapine in combination with other antipsychotic drugs, Zink [75] argues that trials were generally favourable, although only one study randomised its patients. On the other hand, antipsychotic polypharmacy has been investigated as a strategy to ameliorate problematic antipsychotic drug side effects, as well as to improve the effectiveness of monotherapy, and this particularly applies to clozapine. For instance Henderson et al. [76] report that an open study adding aripiprazole to clozapine reported some improvements in weight, cholesterol and triglycerides. There was no improvement in symptoms however. Similarly, Karunakaran et al. [77] found that the combination may induce weight loss in 75% of patients, and allow the clozapine dose to be reduced by a fifth.

Regarding safety issues, Baandrup et al. [78] concluded that antipsychotic polypharmacy did not contribute to the death rate from natural causes in elderly patients, although benzodiazepines with long half-lives did so.

Augmentation with Other Psychotropic Drug Classes

Mood Stabilizers: Lithium and Anticonvulsant Drugs

Prekumar and Pick [79] state that a recent meta-analysis returned a disappointing perspective, that evidence in favour of lamotrigine augmentation was not robust. Goff et al. [80] added that a later review of 2 placebo controlled trials was no more hopeful. Even so, Zoccali et al. [81] proposed that a fairly small double blind placebo controlled RCT of lamotrigine and clozapine reported general symptomatic and some cognitive benefits.

Tiihonen et al. [82] state that there was a quite large effect size of 0.7 against placebo in the reduction of positive and negative symptoms compared with another anticonvulsant, the glutamate antagonist topiramate, in a crossover randomised double blind trial. Sajatovic et al. [83] reported that there is recent evidence from one small open study that extended release valproate semisodium induced statistically significant reductions in psychotic and depressive symptoms in older patients, and increased global function scores. However Schwarz et al. [84] stated in their Cochrane review of augmentation with valproate that there was no evidence to support its use, although there might be some effects on aggressiveness.

Citrome [85] concluded from a recent review of the use of lithium and anticonvulsants as adjuncts in schizophrenia that, despite promising initial studies, later work did not confirm a robust advantage. There was little to support the use of either class of drug in treatment resistant or aggressive patients. However it was recommended that lithium or anticonvulsant drugs may be tried on an individual patient basis, but the disadvantages of adverse effects and lack of efficacy should lead to discontinuation as appropriate. Leucht et al. [86, 87] suggest that previous systematic reviews underpinned this, further suggesting that while there may be utility in the treatment of schizoaffective patients with lithium, carbamazepine augmentation could not be recommended routinely. This work partly echoed a slightly older perspective: Berle and Spigset [88] note that lithium and carbamazepine appeared worth trying in aggressive patients, and lithium in patients with affective symptoms. However Kelly et al. [89] state that neither lithium nor valproate added to clozapine in treatment resistant schizophrenia was efficacious. By contrast, Tiihonen et al. [90] found that lamotrigine was efficacious in clozapine-resistant schizophrenia: “a substantial proportion of these most severely ill patients appeared to obtain clinically meaningful benefit from this combination treatment”. The “number needed to treat” was 4.

Antidepressant Drugs

In the treatment of depression in schizophrenia, Esen-Danaci and Aydemir [91] found preliminary evidence that venlafaxine seems as effective in these patients as

it is in depressed patients without schizophrenia. Similarly, citalopram was investigated as an adjunct for the treatment of subsyndromal depression in middle aged and elderly patients in a randomised controlled trial. Zisook et al. [92] reported that active treatment was significantly superior not only for depression, but also for negative symptoms and quality of life in general. Silver et al. [93] argue that specific serotonin reuptake inhibitors (SSRIs) as a class are worth trying in patients with negative symptoms, although Sepehry et al. [94] suggest that their effects may be limited to chronic patients. They have the useful effect of raising serum levels of clozapine while offsetting its sedating side effects. Chertkow et al. [95] point out that there are numerous putative molecular mechanisms for SSRI efficacy in schizophrenia, which may inform drug development in the treatment of negative symptoms. Regarding co-prescription of antidepressant drugs in general for negative symptoms, Rummel et al. [96] conclude that a meta-analysis found evidence for efficacy which was not readily apparent from most of the component studies. Nonetheless, most of the studies utilised conventional rather than atypical antipsychotic drugs, rendering the results difficult to apply to current practice. Citalopram has been trialled in cognitive impairment in schizophrenia, alongside quetiapine: Friedman et al. [97] report that no effects were observed.

Benzodiazepines

Volz et al. [98] state that a recent Cochrane review of benzodiazepines in schizophrenia failed to find evidence of any benefits except to induce short-term sedation in acutely agitated patients, despite the ubiquity of their prescription to patients beyond the acute stage.

Anti-dementia Drugs

Donepezil, an anticholinesterase inhibitor indicated in dementia, was trialled against placebo in a randomised design to augment risperidone in respect of negative symptoms and cognition. Akhondzadeh et al. [99] reported that although there was a significant benefit for negative symptoms, this was dissociated from cognition as the donepezil and placebo groups did not differ on any measure. There is a slightly earlier randomised double blind placebo controlled study of augmentation of haloperidol with donepezil: Lee et al. [100] found significant improvements in negative symptoms, but no effects on cognition. Mazza et al. [101], Fagerlund et al. [102], Erikson et al. [103] and Keefe et al. [104] report that similar studies demonstrated zero or very minor effects on symptoms and cognition. Nevertheless, Risch et al. [105] argue that their double blind placebo controlled randomised crossover trial reported significant benefit for negative symptoms. Even so, Guillem et al. [106] note that a study using a drug of the same class, rivastigmine, failed to demonstrate more than a trend to differences in reaction time using a placebo controlled

randomised crossover design, despite demonstrable effects of rivastigmine on event related potentials.

This emphasises that the association between neurophysiological and functional effects is not straightforward: Sharma et al. [107] found that these results replicated an earlier study with a negative outcome. Indeed, Dyer et al. [108] reported that in another study of a similar antidementia drug, galantamine in high doses, galantamine was actually inferior to placebo on neurocognitive measures. Lee et al. [109] similarly noted that their study of galantamine failed to find any effects on cognition or symptoms: Lee and Kim [110] went on to re-iterate their conclusions from a preliminary study, that galantamine did not dramatically improve measures of cognition or psychopathology. Nevertheless, Schubert et al. [111] state that a small earlier study reported improvements in memory and attention.

Memantine, a noncompetitive NMDA antagonist indicated in moderate to severe Alzheimer's disease, has been investigated in symptoms and cognition in schizophrenia: Lieberman et al. [112] demonstrated that it was not efficacious, and induced more side effects than placebo.

A novel cholinergic strategy examined the effect of an agonist of alpha7 nicotinic acetylcholine receptors (alpha7 nAChRs) in schizophrenia. Cytidine diphosphocholine (CDP-choline), a dietary source of the alpha7 nAChR agonist choline, and galantamine (24 mg/d), a positive allosteric modulator of nAChRs that was prescribed to prevent choline from becoming a functional antagonist, were given together to 6 patients alongside their usual treatment. Deutsch et al. [113] reported that 5 patients reduced their PANSS scores and 3 of these requested that the treatment be continued beyond the 12 week trial period. The combination was well tolerated and the authors concluded that further trials were indicated.

Drugs for Substance Abuse

Substance abuse is a huge and escalating clinical problem in treating patients with schizophrenia. There is very little data on pharmacological strategies, indeed, substance abuse and dependence constitute exclusion criteria in most research trials. Wobrock and Soyka [114] conclude that naltrexone and tricyclic antidepressant drugs may reduce craving and overall consumption of substances. However, the poor safety profile of antidepressant drugs in overdose, alongside the increased risk of completed suicide and deliberate self harm in both schizophrenia patients and substance abusers, would militate against their use.

Atomoxetine

Friedman et al. [115] reported that atomoxetine, a norepinephrine reuptake inhibitor indicated in attention deficit hyperactivity disorder, had no effects on cognitive impairment in schizophrenia.

Augmentation and Supplementation on a Theoretical Basis

Purinergic Drugs

It has been proposed that an anomaly of the purinergic system, specifically a deficit in adenosinergic activity, could be implicated in the pathophysiology of schizophrenia. Increased adenosinergic transmission is thought to reduce the affinity of dopamine agonists for dopamine receptors. Adenosine is believed to modulate glutamatergic systems as well, with trophic and neuroprotective roles related to neurodevelopment and possibly to susceptibility to environmental factors. Lara and Souza [116, 117] propose that pharmacological treatments enhancing adenosinergic activity could be effective in schizophrenia. There is a randomised double blind placebo controlled study of augmentation with propentofylline, which increases extracellular adenosine, compared to placebo when added to risperidone. Salimi et al. [118] report that active treatment proved superior for positive symptoms and general psychopathology. The same group and other investigators have also trialled allopurinol, a xanthine oxidase inhibitor which may increase circulating pools of adenosine. This ought to modulate and attenuate dopaminergic neurotransmission. There is some preliminary evidence for the effectiveness of allopurinol [119–121]. However Dickerson et al. [122] note that the latest small but double-blind placebo controlled RCT reported that only 1 in 8 patients achieved a response, although none of the placebo treated patients did.

Anti Inflammatory/Immunological Drugs

To investigate suppression of pro-inflammatory cytokines, a strategy for which Monji et al. [123] suggest there is some theoretical evidence in schizophrenia, the NSAID celocoxib was added to risperidone in chronic patients. Akhondzadeh et al. [124] found superiority over placebo for positive symptoms and general psychopathology. Riedel et al. [125] argue that earlier work demonstrated that the effects were limited to patients with recent onset of schizophrenia. Laan et al. [126] reported that a study of the NSAID acetylsalicylic acid was planned at about the same time, and is presumably ongoing.

Sexual Hormones

There is some circumstantial evidence that estrogen ought to be useful as an adjunct in schizophrenia owing to potential neuroprotective and antidopaminergic actions, but Mortimer [127] states that trials have been disappointing and the risks not insubstantial. Elias and Kumar [128] note that the position with augmentation with male sexual hormones is similar. Bergemann et al. [129], Ko et al. [130] and Ritsner et al. [131] have continued to investigate the effects of such hormones on tests of cognitive function, but the relevance of any effects to clinical management is undetermined.

Ko et al. [132] found that their short study suggested benefits of testosterone for negative symptoms. Nevertheless, this work remains preliminary, and its significance undetermined.

Antihistaminergic Drugs

Mancama et al. [133] and Ito [134] argue that there is evidence of histaminergic pathophysiology, possibly an overactivity, in the brain in chronic schizophrenia. There is a small open trial comparing famotidine, a histamine H2 receptor antagonist used in duodenal ulcer, with placebo. Farzin et al. [135] report that symptoms overall reduced on famotidine and not placebo: there are older case reports and small trials from the early 1990s.

Serotonin Antagonism

Serotonin antagonism is thought to comprise a useful action in schizophrenia in terms of minimising extrapyramidal side effects and possibly contributing to the treatment of negative symptoms. Indeed, most atypical antipsychotic drugs are serotonin antagonists. The 5HT2A/2C antagonist ritanserin has been utilised as an adjunct to risperidone in a recent double blind placebo controlled RCT: Akondzadeh et al. [136] state that previous work was inconsistent, however their study reported a significant effect on negative symptoms. There is a randomised double blind placebo controlled study of augmentation with ondansetron, a 5HT-3 receptor antagonist, versus placebo in negative symptoms and visuospatial memory function. Akondzadeh et al. [137] reported statistically significant improvements in both domains, but no there is no data on functional outcome. Zhang et al. [138] found that in their double blind placebo controlled RCT of treatment resistant patients, ondansetron reduced side effects as well as symptoms.

Cortisol Antagonism

There is one trial of the glucocorticoid receptor antagonist mifepristone in symptoms and cognitive impairment: the authors Gallagher et al. [139] suggest that hypercortisolaemia may be implicated in schizophrenia. Unfortunately no effects were observed. The authors commented that further work should identify patients with proven hypothalmic-pituitary- adrenal axis dysfunction. Following more recent work, Gallagher et al. [140] found that mifeprisone does effectively reduce cortisol levels.

Nitric Oxide Deficiency

Nitric oxide has been implicated in pathophysiological theories of schizophrenia: Oliviera et al. [141] concluded that well designed studies have implicated a disruption in nitric oxide mediated neurotransmission. Miyaoka et al. [142] completed a small pilot study of the caspase inhibitor antibiotic minocycline, which decreases

inducible nitric oxide synthase, they reported robust clinical improvements after 4 weeks.

Retinoid Dysregulation

There is a hypothesis that retinoid dysregulation may be relevant to schizophrenia: Goodman [143] states that the transcriptional activation of the dopamine D2 receptor gene and numerous other schizophrenia candidate genes is regulated by retinoic acid. There is a pilot study of betaroxene, a synthetic retinoid, in 25 patients: Lerner et al. [144] demonstrated significant improvements after 6 weeks treatment alongside the usual antipsychotic drug. The authors concluded that a double blind placebo controlled trial was warranted.

Miscellaneous

Olanzapine

According to a review of studies of the augmentation of olanzapine with glycine, antidepressants and mood stabilisers, Zink [75] states that these strategies were generally useful in reducing both positive and negative symptoms in reasonably well designed trials.

Mirtazapine

There is one double blind placebo controlled RCT of the potentiation of the antipsychotic effects of conventional antipsychotic drugs by the antidepressant mirtazapine: Joffe et al. [145] demonstrated a robust effect, with the mean reduction in symptoms on active treatment at 17.6% approaching the 20% response threshold routinely utilised in clinical trials. Further studies utilising atypical antipsychotic drugs are awaited. There is one study of mirtazapine augmentation of clozapine, which reported significant improvements in cognition despite no effects on psychosis or depression: Chiaie et al. [146] suggest that mirtazapine, in its enhancement of noradrenergic and serotonergic function, has some similarities to clozapine. The notion that the addition of mirtazapine, an established and well tolerated drug, could turn other antipsychotic drugs into clozapine without the neutropenia, is highly attractive.

Modafinil

There has been interest in the ability of the narcolepsy drug modafinil to reverse antipsychotic induced sedation and fatigue, and possibly to treat negative symptoms and alleviate cognitive deficits in schizophrenia. However Saavera-Velez et al. [147] found that two studies found no effect on negative symptoms and only one of four showed any effect on sedation and fatigue. Half of six studies demonstrated

some cognitive improvements but their functional relevance was not determined. Furthermore exacerbation of psychosis occurred in 6% of patients. Even so, Peloian and Pierre [148] reported significant "global improvement" in their study, despite no effect on negative symptoms.

Selegiline

There has been some interest in selegiline, an MAOI-B inhibitor, in treating negative symptoms of schizophrenia. The results of several studies were contradictory, however. Amiri et al. [149] found selegiline significantly superior to placebo when added to risperidone in their recent small double blind placebo controlled RCT. Larger trials were recommended, although Fohey et al. [150] were pessimistic following their systematic review of all studies available.

Pergolide

Roesch-Ely et al. [151] published a case report of the successful use of pergolide, a mixed D1/D2 agonist, in a patient treated with amisulpride who continued to suffer depressive and negative symptoms.

Valacyclovir

Dickerson et al. [152] made an attempt to treat cytomegalovirus seropositive patients with the antiviral drug valacyclovir using open randomised methodology: there were no effects.

S-Adenosyl Methionine

S-adenosyl methionine (SAM-e) increases catechol-O-methyltransferase (COMT) enzyme activity, which may ameliorate aggressive symptoms in certain patients. SAM-e has been tested in patients with the low activity version of COMT, which it enhances, in a very small ($n = 18$) but randomised double blind placebo controlled RCT. Strous et al. [153] reported some improvements in aggression, quality of life and, in female patients, depression.

Ginkgo Biloba

There is one small placebo controlled study of ginkgo biloba for negative symptoms: Doruk et al. [154] found a small advantage for the active treatment, but of questionable clinical significance.

N-Acetyl Cysteine

Brain glutathione levels are decreased in schizophrenia: n-acetyl cysteine has been trialled in an attempt to increase these levels and reduce symptoms in a placebo

controlled randomised RCT. Judd et al. [155] reported statistically significant but clinically marginal decreases in total PANSS scores.

Vitamin C

There is one double blind placebo controlled RCT of vitamin C in schizophrenia, on the grounds that oxidative stress may be relevant to pathophysiology. Dakhale et al. [156] reported a significant advantage for vitamin C in the improvement of symptoms.

Integrating Multiple Mechanisms

Clozapine, a superior antipsychotic drug, targets multiple versions of a wide variety of receptors. Similar antipsychotic drugs such as asenapine, lurasidone and alstonine which also manifest such "rich pharmacology" may prove safe and effective despite their lack of specificity and the difficulties in explaining their effects. Many drugs of this type approximate to clozapine in a diversity of animal models, yet none is superior in patients to more restricted alternatives, and none emulates clozapine in treatment resistance. Indeed, none of the receptors interacted with by clozapine has been demonstrated to hold the key to superior efficacy. Choi et al. [157] argue that clozapine has unrelated properties, such as its effects upon calcium channel gating, which result in global therapeutic effects on neuronal excitability.

Nevertheless, the notion of a drug which targets a relevant combination of receptors known to mediate therapeutic action has been proposed. Deng et al. [158] point out that it may be possible to identify therapeutic targets such as the D2 receptor and separate these from "toxic targets", such as the histamine H1 and H3 receptors in respect of weight gain, for instance.

Roth [159] propose that therapeutic targets could be "designed in" and toxic targets "designed out" of new antipsychotic drugs. Graham et al. [160] mention ongoing attempts to vary the chemical structure of ziprasidone so that its affinities conform to what is known about efficacy and safety, particularly regarding QTc prolongation.

Genomics based screening techniques which look for novel drugs on the grounds that they mimic the gene expression signature of clozapine or other existing antipsychotic drugs may hold promise. Thomas et al. [161] state that drug induced changes in gene expression converge with alterations in gene expression observed post-mortem: all are relevant to synaptic machinery, myelin function and protein metabolism. Nonetheless there is a potential limitation, in that drug discovery may be limited to the identification of yet more "me too" drugs. Even so, it has to be said that a new clozapine, without the neutropenia, weight gain, sedation, salivation and lowered seizure threshold, available in oral long-acting or very long-acting implantable form, would be well worth having.

Pani [162] proposes an alternative approach, individualised antipsychotic treatment which takes into account pharmacokinetic as well as pharmacodynamic factors. Ericson [163] indicates that this extends the analogy to that of the "specially

engineered shotgun load". The approach is predicated upon the identification of "treatment moderators" which specify for whom or under what conditions a treatment works, and "treatment mediators" i.e. therapeutic mechanisms. Cluster analysis could be used to identify subsets of patients differentially responding to treatment mediators according to treatment moderators. Sets of criteria could then be determined with the objective of improving outcomes through individualised prescribing. A current simple exemplar would be the improved outcome with clozapine in the cluster of treatment resistant patients compared to other antipsychotic treatment: the moderator is treatment resistance and the mediator is the relevant therapeutic mechanisms (still to be determined) of clozapine.

Conclusions and Future Directions

Despite its poor tolerability, we already have a magic shotgun: clozapine. The author would recommend at least considering clozapine if two first line antipsychotic treatments are inadequate, particularly for core positive and negative symptomatology, when non-compliance and substance abuse have been excluded. The problem with clozapine is that it is such an onerous option for both patient and clinician that it may seem entirely reasonable to try augmentation first. There is not much argument against this, although repeated trials of polypharmacy will become harder to justify with each successive attempt. Indeed, Honer et al. [74] argue that trials of polypharmacy may be a factor contributing to the underutilization of clozapine and long delays in initiating clozapine monotherapy.

Beyond interference with receptor modulated signal transduction through ordinary antipsychotic drugs, it may be that gene-based interventions, or even action before disease onset will be necessary to ameliorate abnormal neuronal migration, pruning and connectivity. Gray and Roth [164] point out that these deficits are unlikely to respond to simple pharmacological approaches. Finally, Marino et al. [165] draw attention to the fact that the discovery of numerous if tentative genetic associations with schizophrenia has not yet led to the identification of new targets for intervention. If the phenotype of schizophrenia eventually proves to be the result of aberrant, irrevocable neurodevelopment in the earliest years of life, then treatment will only ever be palliative.

Even so, a gratifying amount of high quality, ongoing innovative research presently continues the long running battle waged by scientists and clinicians against schizophrenia. Perhaps a "magic machine gun" will constitute the next stage, and may even win the war.

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Chapter 3
Advancing Neuroprotective-Based Treatments for Schizophrenia

Michael S. Ritsner and Vladimir Lerner

Abstract Schizophrenia is a chronic, severe, and disabling brain disease. About one-third of all patients with *schizophrenia* do not respond adequately to drug treatment. Advances in neuroscience and clinical research have led to the introduction of a novel generation of compounds with neuroprotective properties. Despite numerous animal studies with promising neuroprotective agents, no successful strategy for neuroprotection from functional psychoses has been successfully demonstrated. There are two main targets for neuroprotective therapy: (1) neurodegenerative processes in schizophrenia (e.g. apoptosis, excitotoxicity, oxidative stress, stress sensitization, and alteration of neurosteroids); and (2) phenotypic presentations of illness including psychopathological symptoms, significant decline in cognition, psychosocial functioning and in health related quality of life (HRQL). In this chapter substantial information about clinical trials with neurosteroids, vitamins, and some herbal supplements with neuroprotective properties in schizophrenia is presented. Neurosteroids such as pregnenolone (PREG), dehydroepiandrosterone (DHEA) and their sulfates (PREGS and DHEAS) are reported to have a modulatory effect on neuronal excitability and synaptic plasticity. In addition, vitamins and herbal supplements are important for regular cell function, growth and development. As a rule, vitamins promote the activity of enzymes to improve their efficiency and in this role they are called coenzymes. The herbal supplements are active antioxidants with neuroptective properties. The authors hope that neuroprotective strategies will pave the way to the next generation of antipsychotic, sedative and mood stabilizer medications. The clinical effects of neuroprotective agents clearly merit further clinical trials for the treatment of mental disorders.

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Abbreviations

AA	Arachidonic acid
AIMS	Abnormal involuntary movement scale
BARS	Barnes Akathisia rating scale
BDNF	Brain-derived neurotrophic factor
CANTAB	Cambridge automated neuropsychological test battery
CGI-S	Clinical global impression severity scale
CNS	Central nervous system
CSDS	Calgary scale for depression in schizophrenia
DHA	Docosahexaenoic acid
DHAs	Docosahexaenoic acids
DHEA	Dehydroepiandrosterone
DHEA(S)	Both DHEA and DHEAS
DHEAS	Dehydroepiandrosterone sulfate
DNA	Deoxyrybonucleic acid
DPA	Docosapentaenoic acid
EGb	Extract of gingko biloba
EPA	Eicosapentaenoic acid
EPS	Medication-induced extrapyramidal symptoms
EPUFAs	Essential polyunsaturated fatty acids
ESRS	Extrapyramidal symptom rating scale
FGAs	First-generation antipsychotics
GABA	Gamma-aminobutyric acid
$GABA_A$	Gamma-aminobutyric acid receptor type A
HAM-A	Hamilton scale for anxiety
Hcy	Homoysteine
HPA	Hypothalamic-pituitary-adrenal axis
LDL	Low-density lipoprotein
NMDA	N-methyl-D-aspartate
PANSS	Positive and negative symptom scale
PD	Parkinson's disease
PREG	Pregnenolone
PREG(S)	Both PREG and PREGS
PREGS	Pregnenolone sulfate
PUFA	Polyunsaturated fatty acids
QLS	Quality of life scale for rating the schizophrenic deficit syndrome
SAM	S-adenosylmethionine
SANS	Scale for the assessment of negative symptoms
SAPS	Scale for the assessment of positive symptoms
SAS	Simpson-Angus scale

SD	Standard deviation
SGAs	Second-generation antipsychotics
SOD	Superoxide dismutase
TD	Tardive dyskinesia

Introduction

Schizophrenia is a chronic and disabling mental disorder characterized by positive, negative and mood symptoms, impaired capacity for coping, elevated distress and a significant decline in cognition, quality of life and psychosocial functioning. Understanding the etiology and pathogenesis of schizophrenia is a major challenge facing psychiatry. Treatment of schizophrenia patients typically includes pharmacotherapy with antipsychotic agents together with psychosocial interventions.

Antipsychotic agents ameliorate symptoms in the early phases of disease but become less effective over time, as the underlying disease progresses. Despite the effectiveness of antipsychotic medications in the treatment of schizophrenia, about one-third of all patients with schizophrenia do not respond adequately to pharmacotherapy. Although antipsychotic agents are an indispensable component of the treatment, the development of more effective treatments is an important and desirable goal.

This chapter focusses on evidence from clinical and basic science studies supporting a role of neurosteroids, several vitamins and supplements as potential neuroprotective compounds.

Neuroprotective Treatment Strategy

By definition, neuroprotection is an effect that may result in salvage, recovery or regeneration of the brain, its cells, structure and function. The neuroprotective approach is a treatment paradigm, that is theoretically based on both neurodevelopmental and neurodegenerative models of schizophrenia [1–5]. This approach aims to protect against gray matter loss and slow functional decline following the onset of psychosis, and to maintain functional integrity of the brain in response to neurobiological stress. Neuroprotective therapy is the administration of an agent (medication, compound etc) that aims to reverse or prevent further brain damage. During the past few years research has focused on developing neuroprotective agents for the treatment of various degenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, and glaucoma. Regarding schizophrenia and related disorders some neuroprotective agents (e.g., erythropoietin, glycine, D-serine, neurosteroids, memantine, celecoxib, and others) are currently being evaluated as add-on therapies [6, 7]. Although the molecular mechanisms of neurodegeneration and pathogenesis of schizophrenia remain largely

unknown, a significant body of literature indicates that the main mechanisms implicated in the disease process may include apoptosis (programmed cell death [8]), excitotoxicity, oxidative stress, stress and others.

Apoptosis is a one of the most recent mechanisms implicated in the pathophysiology of schizophrenia [9, 10]. Several postmortem studies have demonstrated that apoptotic vulnerability may be increased in the brains of patients with chronic schizophrenia, even though there is no active cell death [3, 11].

Oxidative stress has been defined as 'a disturbance in the pro-oxidant–antioxidant balance' in favour of the former, leading to potential damage [12, 13]. Oxidative stress can cause cellular damage and subsequent cell death because the reactive oxygen species oxidize vital cellular components such as lipids, proteins, and DNA. Oxidative stress has been implicated in the pathophysiology of many neurodegenerative diseases, in particular, Parkinson, Huntington, and Alzheimer disorders, amyotrophic lateral sclerosis, and other disorders. There is evidence suggesting that peripheral activities of antioxidant enzymes and lipid peroxidation are abnormal in schizophrenic subjects. In particular, decreased activity of key antioxidant enzymes in schizophrenia [14], and increased lipid peroxidation products and altered defence systems in both chronic and drug-naive first episode schizophrenic patients [15]. The accumulated results indicate that oxidative stress is integral to this disease and not the result of neuroleptic treatment [16]. According to modern opinion, antioxidant treatment may represent a novel therapeutic approach for schizophrenia. Schizophrenia patients have a deficit in antioxidant defense that may leave highly vulnerable brain cells open to attack by reactive oxygen species [17]. Research has revealed that schizophrenia patients and control participants had similar levels of oxidants, but patients with schizophrenia had lower levels of antioxidants [16, 18–21]. Plasma total antioxidant capacity has been found to be significantly lower in schizophrenia patients than in normal controls, regardless of clinical variables such as relapse status and antipsychotic drug treatment. Also, a previous report found that the total antioxidant capacity is inversely correlated with reduction of psychopathology suggesting pathophysiological significance in schizophrenia [16]. It has been proposed that there are abnormalities in major antioxidant levels in patients with schizophrenia, indicating that a reduction in the antioxidant levels is involved in the early stages of schizophrenia regardless of the antipsychotic treatment effect [18]. There is some evidence that an antioxidant supplementation to basic antipsychotic treatment may have a beneficial effect in the management of schizophrenia patients. Many substances, including vitamins such as vitamins B, E and C and nutrition supplements can act as antioxidants.

Excitotoxicity is the pathological process by which nerve cells are damaged and killed by glutamate and similar substances (for review see [22]). Deficits in N-methyl-d-aspartate (NMDA) receptor function play a critical role in the pathophysiology of schizophrenia. Patients who have excitotoxic damage would be expected to have poor outcomes possibly characterized by anatomic evidence of progressive neurodegeneration, pronounced negative symptoms and cognitive deficits, and profound psychosocial deterioration [23]. Blockade of the excitotoxicity process may be brain protective for schizophrenia patients.

Neurosteroids as Neuroprotective Agents

Pregnenolone (PREG), dehydroepiandrosterone (DHEA), and its sulphates (PREGS, DHEAS) are neurosteroids [24], which have neuroprotective and neuropsychopharmacological properties: neuroprotection against apoptosis, NMDA or oxidative damage, promotion of neurite growth, opposition of glucocorticoids, neurite growth, and antagonistic effects on oxidants and glucocorticoids, a modulatory effect on neuronal excitability and synaptic plasticity. They have many functions associated with response to stress, mood regulation and cognitive performance [25–30]. In addition, DHEA and DHEAS inhibit *apoptosis* in human peripheral blood lymphocytes through a mechanism independent of either androgen receptors or estrogen receptors [31]. These neurosteroids demonstrate neuroprotective effects on *NMDA-induced neurotoxicity*. They block the neurotoxic effects of cortisol on hippocampal cells and protect neurons against glutamate and amyloid ß-protein toxicity, and glucocorticoid toxicity; regulate neurogenesis in the hippocampus and modulate the inhibitory effect of increased corticoids on both the formation of new neurons and their survival [32–39]. Thus, these findings suggest that PREG(S), and DHEA(S) may act as endogenous neuroprotective factors. The decline of neurosteroid levels during aging and schizophrenia may leave the brain unprotected against neurotoxic challenges. Therefore, PREG and DHEA may be suitable candidates for the treatment of schizophrenia and schizoaffective disorder patients.

Clinical Trials with Neurosteroids

Since biological actions of PREG and DHEA include neuroprotective and antistress effects, a modulatory effect on neuronal excitability and synaptic plasticity, it is important to examine the alterations of these neurosteroids in schizophrenia and schizoaffective disorders. There is accumulating evidence that alterations in PREG(S) and DHEA(S) may be involved in the pathophysiology of schizophrenia, mood and cognitive disorders [40–42].

Clinical trials with the use of oral DHEA have extensively studied various somatic and neuropsychiatric disorders in healthy elderly and postmenopausal women (see for review [7, 42]). Several randomized, double-blind, placebo-controlled clinical trials were conducted with these neurosteroids for treatment of schizophrenia patients. DHEA augmentations (50–200 mg/day) for a period of 1–12 weeks were examined in cross-sectional and crossover designs [30, 43–49]. Comparative analyses of the obtained findings are presented in a review [30]. Table 3.1 presents the main parameters and results from clinical trials with DHEA and PREG augmentations.

The first randomized, double-blind, placebo-controlled study compared patients receiving DHEA ($n = 15$) and placebo ($n = 12$) and indicated significant efficacy of DHEA augmentation (100 mg/day) after 6 weeks in the management of *negative, depressive, and anxiety symptoms* of schizophrenia [47]. Limitations of the study

Table 3.1 Dehydroepiandrosterone (DHEA) and pregnenolone (PREG) as an adjunctive treatment in schizophrenia and schizoaffective disorders: the main parameters and results from clinical trials [7]

	Participants (daily dose)					Significant effect of DHEA or PREG augmentation compared to placebo			
Study	DHEA	PREG	Placebo	Length of trial (weeks)	Antipsychotics	Symptoms	Cognition	Side effects	Quality of life
[49]	15 (100 mg)	–	12	6	FGAs, SGAs	Negative, depressive, and anxiety symptoms	No data	No data	No data
[47]	15 (100 mg)	–	15	1	FGAs, SGAs	No effect	No data	Extrapyramidal symptoms	No data
[43]	16 (150 mg)	–	15	12	Olanzapine	No effect	No effect	No effect	No data
[48]	55 (200 mg)	–	55	6	FGAs, SGAs	No effect	Visual sustained attention, and motor skills	No effect	No effect
[44]	16 (400 mg)	16 (30 mg), 10 (200 mg)	16	8	FGAs, SGAs	Positive symptoms[b]	Attention and working memory performance[b]	Extrapyramidal symptoms[c]	No data
[51]	–	8[a] (500 mg)	9	8	SGAs	No effect	No effect	No effect	No effect
Total	117 (100–400 mg)	34 (30–500 mg)	122	1–12	FGAs, SGAs	The clinically significant benefits remain unclear.			

Design: a randomized, double-blind, placebo-controlled study [43, 44, 47, 49, 51]; a randomized, double-blind, placebo-controlled crossover study [48]
FGAs – first-generation antipsychotics; SGAs – second-generation antipsychotics
[a]Dosing: 100 mg/day for 2 weeks, 300 mg/day for 2 weeks, and 500 mg/day for 4 weeks
[b]Significant for PREG augmentation, 30 mg/day
[c]Significant for PREG and DHEA augmentations

included small sample size and lack of cognitive, side effect and quality of life assessments.

A second randomized, double-blind, placebo-controlled study investigated the effect of DHEA administration for 7 days on medication-induced extrapyramidal symptoms (EPS) among inpatients with schizophrenia or schizoaffective disorder randomized to receive either 100 mg DHEA or placebo in addition to a constant dosage of antipsychotic medication [43]. The authors concluded that DHEA appears to demonstrate a significant effect on EPS, with improvement observed particularly in Parkinsonian symptoms.

A third randomized, double-blind, placebo-controlled study performed by the same research group included 40 patients with chronic schizophrenia stabilized on olanzapine. Participants received either DHEA (150 mg/day) or placebo augmentation for a period of 12-weeks [48]. Sixteen patients who received DHEA and 15 patients who received placebo completed the study. The analysis *of negative symptoms* measured with the Scale for the Assessment of Negative Symptoms (SANS) did not reveal a significant difference *between DHEA and placebo arms*. DHEA augmentation was not superior to placebo in improving the scores of the Positive and Negative Symptom Scale (PANSS), measures of side effects [the Simpson–Angus Extrapyramidal Symptom Scale (SAS), Barnes Akathisia Scale (BARS), and Abnormal Involuntary Movements Scale (AIMS)], in cognitive performance (Mindstreams battery), and aggressive behavior (the Life History of Aggression scale). After 3 months of DHEA administration no improvements in symptoms of schizophrenia and side effects were detected. In addition, these cross-sectional DHEA trials did not replicate one another in terms of depressive or anxiety symptoms, and in medication-induced adverse side effects. They did not show a consistent and unequivocal significant favorable effect of DHEA administration on negative symptoms compared to placebo.

Next, a randomized, double-blind, placebo-controlled crossover study was conducted in two mental health centers [50] with 55 patients that received either DHEA (200 mg/day) or placebo for 6 weeks following which they were switched to either placebo or DHEA for a further 6 weeks. Patients continued to receive their regular treatment with daily doses of antipsychotic medication kept constant for at least 2 weeks prior to entering the study and throughout the study period. The crossover analysis revealed no statistically significant treatment effect of DHEA on severity of illness symptoms measured by PANSS, side effects, or on quality of life measures compared with placebo treatment. However, this investigation, while preliminary, supports prior findings of some improvement noted in visual sustained attention, and motor skills associated with DHEA administration. DHEA treatment was well tolerated without any serious adverse effects.

Findings from this trial were used for multiple regression analyses for predicting sustained attention, memory, and executive function scores across three examinations from circulating levels of DHEA, DHEAS, androstenedione, and cortisol through DHEA administration in schizophrenia [46, 50]. The findings indicated that circulating DHEAS and androstenedione levels were positive predictors of cognitive functioning, and DHEA level was a negative predictor. Overall, blood neurosteroid

levels and their molar ratios accounted for 16.5% of the total variance in sustained attention, 8–13% in visual memory tasks, and about 12% in executive functions. In addition, effects of symptoms, illness duration, daily doses of antipsychotic agents, side effects, education, and age of onset accounted for variability in cognitive functioning in schizophrenia. Thus, this study suggests that alterations in circulating levels of neurosteroids and their molar ratios may reflect pathophysiological processes, which, at least in part, underlie cognitive dysfunction in schizophrenia [45].

Findings from two pilot clinical trials with PREG augmentation in schizophrenia were recently reported. The first, an 8-week, controlled, double-blind, randomized, parallel-group trial with "low dose" and "high dose" PREG (30 and 200 mg/day, respectively), and 400 mg/day DHEA augmentation of on-going antipsychotics in the treatment of chronic schizophrenia and schizoaffective disorder patients was conducted in two large state referral institutions [51]. Fifty eight patients were randomized and 44 patients completed the trial. Ten patients met criteria for schizoaffective disorders; all other participants met criteria for schizophrenia. After an 8-week period, compared with placebo, PREG administration of 30 mg/day was associated with significant reduction in positive symptom scores, side effects (EPS), and improvement in attention and working memory performance, whereas participants treated with 200 mg/day of PREG did not differ on outcome variable scores for the study period. Patients that received placebo and 30 mg/day of PREG revealed greater improvement than those treated with DHEA in terms of severity of general psychopathology and general functioningHowever, DHEA was superior to placebo in improving EPS. No significant main effect of the type of antipsychotics or type of antipsychotics time interaction on the Clinical Global Impression – Severity scale (CGI-S), PANSS subscale, the Global Assessment of Functioning Scale, Extrapyramidal Symptom Rating Scale (ESRS) or Barnes Akathisia Rating Scale (BARS) ratings was observed for patients that received PREG (30 or 200 mg/day), DHEA or placebo. Interestingly, a significant efficacy of DHEA augmentation was observed with 50–150 mg/day [47, 48], but not with 200 mg/day [44] or 400 mg/day [7]. Moreover, the augmentation of 400 mg/day of DHEA resulted in significantly less improvement of CGI-S, and PANSS general psychopathology sub-scale scores compared to placebo. Therefore, we suggest an inverted-U clinical response on a daily dose of PREG and DHEA augmentations (although there could be other reasons for the inconsistent results: methodological issues, different sample characteristics, different baseline severity of illness, and varying durations of combination treatment). *Negative symptoms and akathisia did not significantly benefit from any treatment*. The administration of PREG and DHEA was well tolerated. Circulatory pregnenolone was found significantly higher among patients treated by both neurosteroids compared to the placebo group; however, it was significantly higher among patients that received 200 mg/day PREG compared to 30 mg/day PREG and the DHEA groups. This study demonstrated no effects of PREG administration on the other hormones measured in this trial, while treatment with DHEA significantly elevated blood levels of PREG (but to a lesser extent than PREG 200 mg/day), as well as DHEA, DHEAS,

androstenedione, 3a-androstane-3a-17b-diol-glucoronide, testosterone, and estradiol compared to PREG-30, PREG-200 and placebo. No between-group differences in the levels of progesterone, 17-OH-progesterone, and cortisol were revealed. The patients that received PREG were not at risk for elevation of androgenic metabolites, such as DHEA, which may in turn potentially predispose them to various disorders such as prostatic hypertrophy in men and hirsutism in women. PREG's treatment effects cannot be explained by an impact of their neuroactive metabolites such as DHEA, DHEAS, androstenedione, 3a-androstane-3a-17b-diol-glucoronide, testosterone, and estradiol. Considering the lack of any significant effect of PREG on the measured hormonal profile in this study, it may be suggested that PREG's therapeutic effects as noted are mediated by other mechanisms, including further potential hormonal influences not investigated in this study. In addition, direct neuromodulatory effects on the $GABA_A$, NMDA, sigma-1, dopaminergic, cholinergic or neurotrophic systems may mediate PREG's effect. Thus, although based on a relatively small sample size, this study suggests that low-dose PREG treatment for 8 weeks, used as an adjunct to antipsychotics, has a valuable ameliorating effect on positive symptoms, attention and memory impairments and antipsychotic-induced extrapyramidal side effects in chronic schizophrenia and schizoaffective patients. These initial results warrant replication in a larger cohort.

A second "proof-of-concept" randomized, placebo-controlled, double-blind trial was initiated in June 2005, and aimed at investigating adjunctive PREG for cognitive and negative symptoms in patients with schizophrenia or schizoaffective disorder that received stable doses of second-generation antipsychotics [52]. Following a 2-week single-blind placebo lead-in, patients were randomized to PREG (100 mg/day for 2 weeks, 300 mg/day for 2 weeks, and 500 mg/day for 4 weeks) or placebo, for 8 weeks. Of 21 patients randomized, 17 patients completed the entire 8-week study post-randomization; one patient randomized to the placebo group completed only 4 weeks of the study ($n = 9$/group). Authors reported that 8 patients that received PREG demonstrated significantly greater improvements in SANS scores (mean change = 10.38) compared with 9 patients treated with placebo (mean change = 2.33, $p = 0.048$, *uncorrected for multiple comparisons*). However, application of the Bonferroni correction to the 8 psychiatric rating scales used in this study (PANSS, SANS, CGI-S, Calgary Depression Scale [CSDS], SAS, BARS, AIMS, Quality of Life Scale for rating the schizophrenic deficit syndrome [QLS]) corresponds to setting the p value a priori at $p < 0.006$ ($p = 0.05/8$). Furthermore, 8 patients randomized to PREG augmentation demonstrated improvement on "affect" subscale scores of SANS (mean change -4.25 ± 1.68 SD) compared with 9 patients that received placebo (mean change 0.22 ± 1.04 SD; $p = 0.035$, *uncorrected for multiple comparisons*). Again, application of the Bonferroni correction to the 5 SANS subscales corresponds to setting the p value a priori at $p < 0.010$. In addition, changes in four other SANS subscales (alogia, avolition/apathy, anhedonia/asociality, and attention), PANSS (negative, positive, and general psychopathology sub-scales), CGI-S, CSDS, SAS, BARS, AIMS, QLS scores, and in mean composite changes in two neurocognitive measures were not significantly different in patients randomized to PREG compared with placebo. Thus, when

Bonferroni correction was applied, improvement on any outcome measure did not reach a significant level ("negative trial"). Over the last few decades, statistical analysis has increasingly been used in medical studies. Nevertheless, the hypothesis test has often been misused and misinterpreted. In addition, the number of subjects required is calculated ("power analysis") because without this calculation, reliable conclusions cannot be drawn from the *P* values. For instance, a conclusion in this study ("Pregnenolone may be a promising therapeutic agent for negative symptoms and merits further investigation for cognitive symptoms in schizophrenia") [52], based on a small sample and nonsignificant difference after Bonferroni correction between PGEG and placebo groups, can lead to unsound clinical judgement.

Overall, the results of six clinical trials with two neurosteroids are based on 117 patients who received DHEA and 34 patients treated with PREG. The clinically significant benefits of both DHEA and PREG augmentations remain unclear. It is crucial to replicate these trials with larger samples of schizophrenia or schizoaffective patients, and for a longer duration of treatment. A gap between *animal studies* and *clinical trials* of neurosteroids may be explained, at least partly, by important differences between rodents and primates in terms of their circulating DHEA and DHEAS concentrations, and suggests that age-related changes within the human DHEA metabolic pathway may contribute to the relative inefficacy of DHEA replacement therapies in humans.

Vitamins as Neuroprotective Agents

Vitamins are known as essential nutrients for human beings. They are natural substances, which are found in living plants and animals. There are 13 essential vitamins divided to two types: nine water-soluble (8 B vitamins and vitamin C) and four fat-soluble (A, D, E and K). A varied diet usually gives you all the vitamins you need to stay healthy. Vitamins do not provide energy (calories) directly, but they do help regulate energy-producing processes. With the exception of vitamin D and K, vitamins cannot be synthesized by the human body and must be obtained from the diet. Vitamins must come from food because they are not manufactured or formed by the body [53, 54].

Each vitamin has a special role within the body e.g. in the regulation of processes such as cell growth and repair, reproduction and digestion. Most vitamins take part as coenzymes in biochemical reactions, which makes them significant components in the central nervous system and derived mental health. Some vitamins have antioxidative effects. Oxidation is defined as the loss of at least one electron when two or more substances interact. This phrase is quite broad and the definition relates to different substances ranging from metals to living tissue. Oxidation can sometimes produce reactive substances known as free radicals that can cause oxidative stress or damage to the cells.

Antioxidants are substances that may protect cells against the effects of free radicals and terminate the chain reaction before vital molecules are damaged.

Although there are several enzyme systems within the body that scavenge free radicals, the principle micronutrient (vitamin) antioxidants are lutein, lycopene, beta-carotene – precursor of vitamin A, vitamins B, C, D and E.

Since antioxidative agents have the ability to stop the free radicals chain of damage, their absence may lead to many serious neurologic disturbances such as stroke, neurodegenerative diseases and peripheral neuropathies. These scientific facts, led to the development of the neuroprotection approach.

The goal of the neuroprotection approach is to limit neuronal dysfunction or death after injury in the central nervous system and an attempt to maintain the highest possible integrity of cellular interactions in the brain resulting in undisturbed neural function.

There is a wide range of neuroprotection products available that can potentially be used in more than one disorder, since many of the underlying mechanisms of damage to neural tissues are similar.

The underlying process, which can explain the pathogenesis of mental disorders, is not yet well understood. There are no clear biological markers of disease in the brain tissue of patients with chronic mental disturbances, in contrast to what is found in the brains of patients with dementia.

Almost every nutritional supplement was assumed to be a neuroprotective agent, however some of them have well-marked properties. A partial list of these substances contains vitamin A, vitamins B, C and E, omega-3, piracetam, L-theanine and others.

Clinical Trials with Vitamins

Vitamin A

Vitamin A (retinol) and its derivatives, referred to generically as “retinoids”, play an essential role in the normal development of many organ tissues of all vertebrates. It participates in important processes, such as normal vision, reproduction, embryonic development, cell and tissue differentiation and immunological functions. Vitamin A influences the cellular life cycle by controlling the expression of some genes, which regulate cell proliferation, differentiation and apoptosis [53].

Retinoid and retinoid-associated signaling plays an essential role in normal neurodevelopment and appears to remain active in the adult CNS. Sato and colleagues evaluated on animal models the neuroprotective potential of vitamin A (all-trans retinol), and its geometric isomers, all-trans retinoic acid and 9-cis retinoic acid in stroke. Vitamin A (retinol) and its derivatives were administered as two intraperitoneal injections immediately prior to and following ischemia. A reduction in infarct volume was observed with all-trans retinol, in a dose-dependent manner: maximum protection was found with a 10 mg/kg dose. A similar protective profile was observed with all-trans retinol, but not the stereo-isomer 9-cis retinoic acid.

Administration of the derivatives 1 h following ischemia did not produce significant protection. Taken together these data suggest a possible use of vitamin A derivatives as an acute neuroprotective strategy for stroke [55].

The complex molecular pathways that mediate the effects of vitamin A and its derivatives are increasingly recognized as a component of the repair capacity that could be activated to induce protection and regeneration in the mature nervous tissue. Malaspina and Michael-Titus have reviewed evidence, which supports the hypothesis of an activation of retinoid-associated signaling molecular pathways in the mature nervous tissue and its significance in the context of neurodegenerative, trauma-induced and psychiatric disorders, at spinal and supra-spinal levels. The authors summarize potential therapeutic avenues based on the modulation of retinoid targets undergoing reactivation under conditions of acute injury and chronic degeneration in the central nervous system, and discuss some of the unresolved issues linked to this treatment strategy [56].

Ann Goodman recently presented a new theory for the pathogenesis of schizophrenia called the retinoid hypothesis of schizophrenia. It is based on retinoid involvement in neurodevelopment [57–60] during embryonic life and regulation of genes thought to be important in the pathogenesis of schizophrenia [61–64]. This retinoid theory is supported by three independent lines of evidence: (1) congenital anomalies similar to those caused by retinoid dysfunction, are found in schizophrenia patients and their relatives; (2) the loci which have been suggestively linked to schizophrenia are the same as the genes of the retinoid cascade (convergent loci); and (3) the transcriptional activation of the dopamine D_2 receptors and numerous other schizophrenia candidate genes are regulated by retinoic acid [65]. Several recent reports at the molecular level now suggest that altered transport and lowered synthesis of retinoic acid may be fundamental mechanisms in schizophrenia [66]. Vitamin A (retinoid) deficiency induces selective memory impairment further supporting the hypothesis in that the fine regulation of retinoid-mediated gene expression is important for optimal brain and higher cognition functions [67]. Animal experiments, which disrupt retinoid-signalling pathways, compromise the regulation of synaptic plasticity and related learning and memory behaviours [68]. These pathways have also been connected with the pathophysiology of Alzheimer's disease, schizophrenia and depression [69–73].

Lerner and colleagues performed an open study [74] with a low dose (75 mg/day) of a synthetic retinoid specifically selective for retinoid X receptors – bexarotene in 25 chronic schizophrenia patients. The researchers hypothesized that bexarotene augmentation to ongoing antipsychotic treatment might have a beneficial effect with the antipsychotic treatment of schizophrenia patients. The results of this study demonstrated a significant improvement in PANSS scores. The authors suggest that further studies are needed to examine the efficacy of bexarotene in a double blind mode with a larger sample size. Anyhow the importance of this study is its possible validation of the retinoid theory, and the connection of vitamin A to the etiology of schizophrenia.

Vitamin B_6 (Pyridoxine)

The main problem of previous studies with pyridoxine was that data were not collected using standard scientific tools, and were based on general impression [75–79]. Unfortunately, these were not controlled studies, and no conclusive clinical trials have yet been undertaken [75, 80, 81]. In order to examine whether vitamin B_6 has therapeutic activity we conducted a clinical trial in patients suffering from refractory schizophrenia and schizoaffective disorder, using a double blind, crossover, add-on design [82].

The study sample included the most severe chronic patients in our mental health center. Vitamin B_6 or placebo was supplemented to ongoing antipsychotic treatment in a double blind, crossover study spanning 9 weeks. All patients had stable psychopathology for at least 1 month before entry into the study and continued treatment with their prestudy psychoactive medications throughout the study. All patients were assessed using the PANSS on a weekly basis. Patients were randomized to receive either placebo or vitamin B_6, starting at 100 mg/day in the first week and increasing to 400 mg/day in the fourth week by 100-mg weekly increments. Five of 15 patients (30%) showed various degrees of improvement. However, these results were not considered statistically positive, because only two of the five patients demonstrated significant clinical improvement. It must be emphasized that the doses of pyridoxine were relatively low (maximum 400 mg/day), and the patients had severe chronic mental disorders that were treatment resistant. Thus, it can not be concluded that vitamin B_6 has absolutely no effect on schizophrenia symptoms. Further studies with larger populations and shorter durations of illness are needed to examine the putative efficacy of vitamin B_6 in the treatment of psychotic symptoms in schizophrenia.

Vitamin C (Ascorbic Acid)

Results of an animal study suggest that vitamin C may block the behavioral response to dopamine and enhance the effects of neuroleptic drugs [83]. Singh and colleagues found that there is an inverse correlation between ascorbic acid intake and the risk of schizophrenia [84]. Even when dietary vitamin C intake is adequate for non-schizophrenia patients, schizophrenia patients may have depressed plasma levels and may demonstrate greatly reduced urinary excretion of ascorbic acid after an ascorbic acid load, suggesting that the utilization of vitamin C in schizophrenia patients may be enhanced [85, 86]. The same group of researchers evaluated schizophrenia patients on the same hospital diet as a control group and found that the schizophrenia patients had significantly lower levels of fasting plasma vitamin C and 6 h urinary vitamin C excretion after an ascorbic acid load test. After administration of 70 mg of vitamin C daily for 4 weeks, there were no differences in plasma vitamin C levels between the schizophrenia and control subjects. However, urinary vitamin

C excretion after the vitamin C load test remained significantly lower in schizophrenia patients. This study supports the hypothesis that schizophrenia patients require higher levels of vitamin C than healthy control subjects for optimum vitamin C status [86].

One of the first significant controlled double-blind trials of ascorbic acid in chronic psychiatric patients was reported in 1963 by Milner. He concluded that "statistically significant improvement in the depressive, manic, and paranoid symptoms-complexes, together with an improvement in overall personality functioning, was obtained following saturation with ascorbic acid" [87].

The beneficial effect of vitamin C in addition to antipsychotic treatment in schizophrenia patients was described in a few case reports [88–90]. In a recent study performed on 48 schizophrenia patients and 40 healthy subjects, Dakhale et al. [92] found that supplementation of atypical antipsychotics with vitamin C improves the outcome of schizophrenia [91].

Another group of researchers reported that supplementation with a combination of omega-3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia [92].

Vitamin D

Vitamin D as a neuroactive compound, a prohormone, is highly active in regulating cell differentiation, proliferation, and peroxidation in a variety of structures, including the brain. The large amount of vitamin D in the brain, prompted the interest of many researchers in its role in mental disorders. One theory claims that vitamin D is a component in the pathogenesis of schizophrenia and that its deficiency plays a role in other mental disorders [93–96]. Yan and colleagues in their study on schizophrenia patients described three novel structural variants of the vitamin D receptor [95].

Since vitamin D is a fat-soluble vitamin and a steroid hormone, it can also inhibit the synthesis of inducible nitric oxide synthase and increase glutathione levels, suggesting a role for the hormone in brain detoxification pathways [97]. Neuroprotective and immunomodulatory effects of this hormone have been described in several experimental models, indicating the potential value of vitamin D pharmacological analogs in neurodegenerative and neuroimmune diseases [97].

In recent years there is increasing interest in the neuroprotective effects of vitamin D [98, 99].

Llewellyn and coworkers published research findings that low serum 25-hydroxyvitamin D is associated with increased cognitive impairment [100].

Old age is often associated with bone fractures and pathologiesas well as age-related mood disorders. The relationship with bone metabolism has been established, and several studies have investigated re a link between vitamin D and depression. Wilkins et al. [101] examined a group of elderly individuals and found mean vitamin D levels of 18.6 nM/L, with a clear vitamin D deficiency (levels < 20 nM/L) among 58% of the subjects. Low vitamin D was robustly associated with the

presence of mood disorder (odds ratio 11.7, 95% CI 2.0–66.9). Vitamin D deficiency has also been associated with depression and anxiety in a cohort of individuals with fibromyalgia [102].

Berk et al. found that a substantially higher proportion of depressed individuals are vitamin D deficient, supporting previously published data [103]. This deficiency is particularly exacerbated for those 70 years or older. Vitamin D supplementation has been shown to have a positive effect on mood and wellbeing, however previous studies were limited by small numbers, short treatment duration, or a lack of a placebo control. A therapeutic role for vitamin D supplementation in the treatment of mood disorders could provide safe, low cost therapy with additional advantages to general and bone health [103].

Grant and colleagues hypothesized that vitamin D is a neuroprotective agent and suggested that it can reduce the risk of developing dementia, Their evidence includes observational and laboratory studies that support a beneficial role of vitamin D in reducing the risk of diseases linked to dementia such as vascular and metabolic diseases, as well as an understanding of the role of vitamin D in reducing the risk of several mechanisms that lead to dementia [104].

Vitamin E (ά-Tocoferol)

Animal studies suggest that alpha-tocotrienol can exert anti-apoptotic neuroprotective action independently of its antioxidant property. Among the vitamin E analogs examined, alpha-tocotrienol exhibited the most potent neuroprotective actions in rat striatal cultures [105].

In another study performed by these researchers, the authors suggest that alpha-tocopherol protects striatal neurons via reduction of oxidative stress, presumably by decreasing intracellular O(2)(–) levels, and at least partly through inhibition of apoptosis [106].

Neuroprotective activity was also investigated in other movement disturbances such as Parkinson's disease (PD). Roghani and Behzadi performed a study on rats in order to investigate the neuroprotective effect of vitamin E and found that administration of vitamin E produces a rapid protective effect on the nigrostriatal dopaminergic neurons in the early unilateral model of PD [107].

Post and colleagues [108] found that vitamin E led to substantial reduction in haloperidol-induced impairment of locomotor activity in rats. They reported that the data indicate the usefulness of vitamin E as an adjunct to haloperidol treatment and provide initial clues about the underlying molecular mechanisms involved in these effects.

D'Souza and D'Souza reported that schizophrenia patients were more susceptible than control subjects to oxidative damage. The also found that antioxidant levels are depleted in schizophrenia patients when compared to normal subjects as evident from decreased levels of vitamins E and C in the plasma. They concluded that adjunctive vitamin E at the initial stages of illness may prevent further oxidative injury and deterioration of associated neurological deficits in schizophrenia [109].

Vitamin B_{12} and Folic Acid

Vitamin B_{12} (cobalamin) is normally involved in the metabolism of every cell of the body, especially affecting DNA synthesis and regulation, fatty acid synthesis and energy production and has neuroprotective activity. Folic acid (folate) influences the rate of synthesis of the neurotransmitters dopamine, norepinephrine, and serotonin, and acts as a cofactor in the hydroxylation of phenylalanine and tryptophan [110–112]. Cobalamin and folate facilitate the production of S-adenosylmethionine (SAM) – the exceptional donor of a methyl-group for various reactions of methylation, by promoting the conversion of homocysteine (Hcy) into methionine. Disturbance of biogenic amine metabolism may lead to various psychiatric disorders. In cases of folate or cobalamin deficiency methionine synthetase activity may be severely impaired, resulting in an elevated plasma total Hcy level [113–115].

A neuroprotective effect of a vitamin B_{12} was found in an animal experiment by Akaike and coworkers. They discovered that chronic exposure to methylcobalamin protects cortical neurons against NMDA receptor-mediated glutamate cytotoxicity [116].

The reported prevalence of a low serum cobalamin level among psychiatric inpatients is between 5 and 30% and of a low serum folate level 10–33% [110, 117–118]. These findings are in contrast with a nonpsychiatric population in which only 3–5% had low cobalamin levels and 5–8% low folic acid levels [119–121].

Deficiency of vitamin B_{12} is known to be a pathogenesis for hematological and neural disturbances. It is less known that deficiency of this vitamin may be related to specific mental disorders. There are some reports regarding relationships between vitamin B_{12} deficiency and psychotic states [110, 122–131]. In a screening study performed by our research group, we found that about 30% of schizophrenic, schizoaffective and organic disorder patients had low levels of vitamin B_{12}. The distribution of diagnoses among those patients varied: about 51% suffered from schizophrenia, almost 17% from schizoaffective and bipolar disorders, and 10% had organic disorders [132].

Vitamin B_{12}, which like folic acid is involved in methylation, has also been shown to help schizophrenia patients [133].

According to some authors, vitamin B_{12} and folic acid help reduce psychotic symptoms, but only at high doses [134]. Research at the psychiatric department at Kings College Hospital in London found that high doses of folic acid are highly effective for schizophrenia patients [135].

A combination of folic acid, vitamin B_6 and B_{12} has been shown to be most effective in improving mental health and lowering the homocysteine levels of schizophrenia patients with high homocysteine levels. Levin et al. [136] recruited 42 schizophrenia patients with plasma homocysteine levels >15micromol/L and randomly assigned them to receive folic acid (2 mg/day), vitamin B_6 (25 mg/day), and vitamin B_{12} (400 mcg/day), or placebo for 3 months in a double-blind, placebo-controlled, crossover design. The researchers found that vitamin therapy lead to decreasimg homocysteine levels compared with placebo. The improvement in schizophrenia symptoms as measured by the PANSS, was significantly greater in the

active-treatment group than in the placebo group ($p < 0.02$). Neuropsychological test results overall, were significantly better after vitamin treatment than after placebo. The results of the present study will hopefully rekindle interest in nutritional treatment of this debilitating disease.

Omega -3

Omega-3 fatty acids are long-chain, polyunsaturated fatty acids (PUFA) found in plant and marine sources. Examples of marine-derived omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Linolenic acid is an omega-3 fatty acid found in plants. Unlike saturated fats, which have been shown to have negative health consequences, omega-3 fatty acids are polyunsaturated fatty acids that have been associated with many health benefits. It may prove to be efficacious in a number of psychiatric disorders. Evidence suggests that omega-3 fatty acids may have beneficial effects for schizophrenia patients [137].

Reduced levels of membrane essential polyunsaturated fatty acids (EPUFAs), namely, arachidonic acid (AA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acids (DHAs), and their association with psychopathology have been consistently reported in both chronic-medicated schizophrenic patients as well as in never-medicated patients soon after the first episode of psychosis [92].

There is evidence from double-blind placebo-controlled trials that omega-3 fatty acids might prevent conversion from a prodromal state into first episode psychosis, and reduce the need for antipsychotic agents in first episode patients. Results concerning chronic and acutely relapsing schizophrenia patients have been mixed [138].

An early open-label study of omega-3 PUFA in schizophrenia reported significant improvement in both schizophrenia symptoms and tardive dyskinesia (TD) [139]. These beneficial effects were confirmed in early double blind placebo controlled trials [140]. The authors performed two double blind studies. In the first trial, 45 schizophrenia patients with psychotic symptoms on stable antipsychotic medication were treated with either EPA or DHA or placebo for 3 months. The total PANSS scores significantly improved in the group treated with EPA in comparison to DHA and placebo. EPA was significantly superior to DHA for positive symptoms. In the second placebo-controlled study, EPA was used as monotherapy, though the use of antipsychotic drugs was still permitted if clinically imperative. By the end of the study, all 12 patients on placebo, but only eight out of 14 patients on EPA, were taking antipsychotic drugs. Despite this, patients taking EPA had significantly lower scores on the PANSS rating scale by the end of the study. The researchers concluded that EPA may represent a new treatment approach to schizophrenia, and further investigation by large-scale placebo-controlled trials is warranted. As a result subsequent studies have focused on EPA. To date 9 trials of EPA in schizophrenia were published. They were divided into studies including young people at ultra-high risk of developing psychosis, those who developed first episode psychosis,

and those patients with established chronic schizophrenia. The only placebo controlled trial in ultra-high risk subjects provided evidence that EPA rich omega-3 fatty acids can reduce the risk of these subjects developing overt psychosis [141]. Two studies conducted in first episode patients [140, 142] can be interpreted as showing an antipsychotic-sparing effect of omega-3 fatty acid treatment. Studies in chronic schizophrenia produced mixed results: 3 studies reporting benefits from EPA enriched oil in either the primary or secondary analysis of data [140, 143, 144], two studies showing no benefit of EPA over placebo [145, 146], and one study in acutely relapsing schizophrenia showing that EPA alone led to a significantly worse outcome than placebo treatment [147]. In all of these studies, EPA rich oil was given at the doses from 1.2 to 4 g in addition to ongoing antipsychotic medication.

Thus, to date, there are no clear results regarding the efficacy of omega-3 in schizophrenia patients. Future placebo-controlled trials need to be conducted with a comparison group receiving fatty acid supplements alone, in larger study samples with both chronic and treatment naïve patients, and for longer durations of treatment while the dietary intake is monitored.

Ginkgo Biloba

The ginkgo tree belongs to the botanical family of Ginkgoceae. It is among the oldest living species on this planet. Ginkgo biloba is a dioecious tree with a history of use in traditional Chinese medicine Its name comes from the Chinese words *sankyo* or *yin-kuo*, which means a hill apricot or silver fruit, due to their apricot shaped mature fruits and yellow color [148]. Although the seeds are most commonly employed in traditional Chinese medicine, in last years standardized extract of gingko biloba formulation (EGb 761) is the most used form of supplement for cognitive disturbances and has been widely sold as a phytomedicine in Europe and as a dietary supplement in the United States [149].

The Ginkgo leaf extract includes two main pharmacologically active groups of compounds – the flavonoids and the terpenoids [149]. These compounds are known to act mainly as antioxidants/free radical scavengers, enzyme inhibitors, and cation chelators [150].

Ginkgo leaf extract has shown beneficial effects in treating neurodegenerative diseases such as Alzheimer's, cardiovascular diseases, cancer, stress, memory loss, tinnitus, geriatric complaints such as vertigo, age-related macular degeneration, and psychiatric disorders such as schizophrenia [151]. It has been suggested that EGb may enhance the efficiency of antipsychotics especially on positive symptoms in patients with chronic schizophrenia and reduce serum superoxide dismutase (SOD) levels.

In a double-blind, placebo-controlled study, Zhou et al. [152] explored: the association between schizophrenia symptoms and SOD and investigated the effect of the classic antipsychotic haloperidol plus EGb on SOD. The sample consisted of 54 patients with chronic refractory schizophrenia. Twenty seven patients were treated with haloperidol plus EGb and 27 received haloperidol plus placebo. SOD levels

of these patients were measured before and after treatment and compared with the levels of 25 healthy volunteers. Therapeutic efficacy was assessed using the Scales for Assessment of Positive and Negative Symptoms (SAPS, SANS) The results of this trial revealed that patients treated with haloperidol plus EGb improved significantly as demonstrated by scores from both SAPS and SANS, while those treated with haloperidol and placebo showed improvement only on SANS scores. The authors suggested that EGb may enhance the efficacy of the classic antipsychotic haloperidol on schizophrenia, especially on positive symptoms. They assumed that an antioxidant efficacy of EGb is involved in the therapeutic mechanism [152].

Atmaca et al. [153], evaluated the therapeutic effect of EGb and examined its effect on the levels of antioxidant enzymes in 29 schizophrenia patients treated with olanzapine. The subjects were randomly assigned to the two groups: olanzapine plus EGb and olanzapine monotherapy. The results of this study showed that EGb might enhance the efficiency of antipsychotics, particularly on positive symptoms, in schizophrenia patients. These results were supported by Knable, who enrolled refractory schizophrenia patients in his study [154].

Zhang et al. investigated the effects of EGb administration on T lymphocyte subsets and SOD levels in treatment resistant schizophrenia patients [155]. In this a double-blind placebo-controlled, parallel-group trial 109 schizophrenia inpatients, were randomly assigned to either 360 mg/day of EGb plus a stable dose of haloperidol (0.25 mg/kg/day) or placebo plus the same dose of haloperidol for 12 weeks. After 12-weeks of treatment a significant decrease in SOD levels in the EGb group was revealed. The authors concluded that EGb may improve the decreased peripheral immune functions in schizophrenia. The beneficial effects of EGb on the immune systems and the improvement of schizophrenia symptoms may be mediated through its antioxidant activity [156].

L-theanine

L-theanine (gamma-ethylamino-L-glutamic acid) is a biologically active natural product, present almost exclusively in the tea plant (Camellia sinensis), where it is typically found in 1–2% of dry weight [157]. L-theanine can pass the brain-blood barrier and it has various neurochemical effects on the brain [158–160].

The main effect of theanine is neuroprotective. The neuroprotective effect of theanine is mediated, at least in part, by gamma-aminobutyric acid ($GABA_A$) receptors [161]. Kakuda and colleagues [162] suggest that the mechanism of the neuroprotective effect of theanine is related not only to the glutamate receptor, but also to other mechanisms such as the glutamate transporter. The antioxidant activity of L-theanine has been studied in regard to its effect on the oxidation of low-density lipoprotein (LDL) cholesterol. In vitro testing using malondialdehyde as a marker of lipid peroxidation, demonstrated inhibition of LDL oxidation with theanine, although the effect was weaker than the potent antioxidant effect of green tea polyphenols [163]. Thus, L-theanine displays a neuropharmacology suggestive

of a possible neuroprotective, psychological stress, and cognitive enhancing agent and warrants further investigation in animals and humans.

It was found that the absorbed L-theanine is transported into the brain through the blood–brain barrier via the leucine-preferring transport system [164]. After passing through the blood brain barrier, theanine is not converted to glutamate by brain-type glutaminase and instead exists as a parent compound [165, 166]. It reverts back to its guise as a glutamate mimic and binds to a number of different types of glutamate receptors on nerve cells, although with considerably less affinity than glutamate itself [162]. Recently, Sadzuka et al. [167] supported the notion that L-theanine acts on the brain-neuron system.

Whereas historically, L-theanine has been shown to have relaxing properties [168, 169], it also has a reputation for counteracting the anxious jitters associated with caffeine without interfering with its ability to fight fatigue or sharpen mental focus [170, 171], however, the anxiolytic effects of theanine have not been established scientifically in animal or human studies. The pharmacological effects of L-theanine reported in animals suggest that it may have some anxiolytic properties, given that both serotonin and GABA play a fundamental role in the neurobiology of anxiety and are molecular targets in the treatment of various anxiety disorders [172].

Supporting the preclinical pharmacological effects of L-theanine, one electrophysiological study using healthy human subjects reported possible relaxing effects of L-theanine (200 mg), as indicated by increased alpha activity in the occipital and parietal cortex [173].

L-Theanine has become a promising candidate for management of schizophrenia because L-theanine may influence neurotransmitters in the brain such as GABA, dopamine, and serotonin [164, 174], and ameliorate attention and learning [168], and emotional distress [175].

Our research group hypothesized that L-theanine augmentation to ongoing antipsychotic therapy might improve both psychotic symptoms and cognitive performance in chronic schizophrenia and schizoaffective disorder patients, in comparison to placebo. We thus performed the first a study to examine the efficacy and tolerability of L-theanine as add-on antipsychotic treatment in patients with schizophrenia and schizoaffective disorders.

Sixty patients participated in an 8-week, double-blind, randomized, placebo-controlled study. Four hundred mg/day of L-theanine or placebo were added-on to ongoing antipsychotic treatment. The outcome measures were the PANSS, Hamilton Scale for Anxiety (HAM-A), neurocognitive (CANTAB) and general functioning, side effects and quality of life. Forty patients completed the study protocol. The study demonstrated that compared with placebo, L-theanine augmentation is associated with reduction of anxiety, positive, and general psychopathology scores measured by the HAM-A scale and by the PANSS three-dimensional model, respectively. According to the five-dimension model of psychopathology, L-theanine produced significant reductions on PANSS positive, and activation factor scores compared to placebo. The effect sizes (*d*) for these differences ranged between modest to moderate (0.09–0.39). PANSS negative and CANTAB task scores, general

functioning, side effect and quality of life measures were not affected by L-theanine augmentation. L-theanine was found to be a safe and well-tolerated medication. The authors assume that L-theanine augmentation to antipsychotic therapy can ameliorate positive, activation, and anxiety symptoms in schizophrenia and schizoaffective disorder patients. Further long-term studies of L-theanine are needed to substantiate the clinically significant benefits of L-theanine augmentation.

Conclusions and Future Directions

Neuroprotection is a modern treatment framework for different mental disturbances. The concept of neuroprotection is the administration of some agents, which offer protection against cell degeneration to the neuronal cells. Many of these compounds are biologically active natural products, either plant extracts or endogenous hormones/peptides/proteins. The majority of neuroprotective agents are antioxidants. There is a growing body of evidence that suggests that neurosteroids, vitamins, and some herbal supplements with neuroprotective properties may improve/assist recovery in schizophrenia or other psychiatric disorders. This may be particularly relevant in first-episode schizophrenia, where antioxidant deficiencies have been observed and the resultant oxidative stress/damage may contribute to the pathophysiology of onset of the disorder. The substances with neuroprotective properties could potentially mediate altered or abnormal neurobiological mechanisms that may be relevant in emerging psychotic disorders.

There is a gap between pre-clinical research that reported neuroprotective properties of candidate neuroprotective agents and clinical results regarding the efficiency of those agents. The pre-clinical research data are usually more promising than the clinical trials. Thus, in clinical trials both the serum levels of neurobiological indicators and efficiency of neurprotective agents should be assessed.

This chapter briefly reviews the use of some neuroprotective substances in the treatment of schizophrenia patients. Findings concerning the efficacy of neuroprotective substancesl remain controversial. Cumulative experience from experimental and clinical trials shows that using a neuroprotective molecule with only one mechanism of action for treatment of a disease acannot influence all aspects of the disease. Further research using a multimodal approach is warranted. It is not uncommon for clinicians to use a polypharmacy approach in the treatment of patients resistant to pharmacotherapy. We can assume that administration of combinations of agents with neuprotective properties may be more effective than treatment with a single substance.

Though the efficacy of the supplements in treatment of schizophrenia and schizoaffective disorder is yet to be established we are impressed that large scale studies are necessary to strengthen the currently available objective data. An important conceptual issue that needs to be addressed is whether neuroprotective agents are effective in prodromal stages or whether they have specific efficacy in the active phases of mental disorders.

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Chapter 4
Prevention and Early Intervention in At-Risk States for Developing Psychosis

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Abstract Indicated prevention is currently one of the most promising approaches to fight the individual and societal burden associated with psychosis, and particularly schizophrenia. Though the number of early intervention studies is still limited, encouraging results have already been reported from pharmacological and psychotherapeutic trials. Furthermore, it has become clear that persons characterized by current at-risk criteria are already ill and do not only need preventive intervention to avoid a possible future outcome, but also treatment for current symptoms. While first early intervention studies had been modelled on treatments for full-blown psychosis, a recent study of Omega-3 fatty acids in preventing transition and improving current symptoms in ultra-high risk subjects indicated that it may be possible to develop benign interventions particularly for the at-risk state, independent of their effectiveness in manifest disease states.

Keywords Prevention of psychosis · Ultra-high risk · Prodrome · Basic symptoms · Early intervention

Abbreviations

APS	Attenuated psychotic symptoms
BLIPS	Brief limited intermittent psychotic symptoms
CBT	Cognitive-behavioral therapy
CT	Cognitive therapy
NBI	Need-based intervention
NNT	Number needed to treat
PUFA	Polyunsaturated fatty acids
RCT	Randomized controlled trial
SGA	Second-generation antipsychotics

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SPI Specific preventive intervention
TAU Treatment-as-usual
UHR Ultra-high risk

Introduction

The individual courses of psychoses, particularly schizophrenia, still show a great variance and, despite all progress in treatment, a considerable number of patients experience a tremendous and chronic loss of functioning and quality of life [1–4]. Furthermore, not only the patients but also their relatives are affected by considerable constraints in their conduct of life and health, including societal stigmatization and discrimination [1, 5–7].

The idea that sustained and substantial success in fighting psychoses could be achieved by an efficient prevention has therefore been repeatedly voiced in psychiatry, particularly with regard to schizophrenia [8–12]. Yet contrary to other medical disciplines, this idea had long not been seized by the majority of scientists and clinicians due to psychiatrists' traditional, wide-spread reservations about the possibility of a valid prediction, particularly of schizophrenia. In 1932, these were summarized by the German psychiatrist Mayer-Gross, who had adopted a much more optimistic position himself: "The detection of the illness in its precursor state, which often spans a prolonged period of time, causes the greatest difficulties. [. . .] Furthermore, it has to be agreed to the general experience that these only gradually emerging changes in mental habitus often escape the observation of others and of self or remain unattended for their pettiness." (p. 295f., translated by FSL). Meanwhile general attitudes have greatly changed, and the objective of prevention of mental disorders has been included into national and international health care policy [13–15]: "Given the current limitations in effectiveness of treatment modalities for decreasing disability due to mental and behavioral disorders, the only sustainable method for reducing the burden caused by these disorders is prevention" [16, p. 14].

An important impulse for today's intensive research on prevention of psychoses was given by advancements in prevention research that, at least theoretically, allow the estimation of the predictive accuracy of at-risk criteria and of the preventive efficiency of interventions within manageable time frames [17, 18]. This development was further supported by a paradigm shift in somatic medicine – from a deterministic approach oriented on well-defined cause-effect-relations towards a probabilistic approach based on risk factors [19]. Alike the elder concept of primary prevention, the new approach primarily aims at decreasing the incidence of a disorder, thereby differentiating between an indicated, selective and universal prevention. As an adaption to mental disorders, the definition of indicated prevention in psychiatry was broadened to enable the development of at-risk criteria that can include clinically significant signs and early symptoms of pathological mental changes, as long as the clinical picture does not meet diagnostic criteria for the manifest disorder [20].

According to the probabilistic approach of indicated prevention, the early signs and symptoms have not to be considered early diagnostic symptoms of an indubitably evolving illness but indicators of an increased risk of developing this illness at anytime in future. As such, each brings about a certain error probability. In this context, early detection has therefore to be regarded as an early *risk estimation* rather than an early *diagnosis*. Hence, indicated prevention is associated with a probability to include persons, who would need no or different interventions. Consequently, it requires a most careful cost-benefit consideration.

Different criteria for the prediction of psychosis have been suggested and evaluated (see Volume II, chapter 9 for details). Today, the most frequently investigated approaches are the "ultra-high risk" (UHR) and the basic symptom criteria. Most published intervention trials, however, have used UHR criteria as intake criteria. Although differing in their operationalization, the UHR criteria generally involve three alternative intake criteria: attenuated positive symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) and a combination of a genetic risk factor with a recent functional deterioration ("trait-state"). Transition to psychosis is commonly defined by the presence of full-blown psychotic symptoms for more than 1 week, yet again, some differences occur across centers (see Volume II, chapter 9 for details).

Prevention Studies

Compared to the number of available treatment studies in schizophrenia, the number of studies investigating the prevention of psychosis is vanishingly small. This is not only a result of the relative recency of this field of research but also of the huge efforts needed to collect sufficient sample sizes and to follow them up for a time long enough to expect a sufficient number of transitions to enable statistical inferences. Thus, it takes years to complete a study. As the following overview will show, current available data are still far from being conclusive. Nevertheless, their short-term results have been encouraging and informative for the next generation of studies, which have just been launched.

Prevention Studies Focusing on Pharmacological Intervention

Three randomized controlled trials (RCT) including antipsychotics have been conducted in UHR samples until now [21–26]. A fourth observational study aimed to evaluate the differential effects of antidepressants and antipsychotics [27]. A fifth study stroke a new path, which may have opened the doors to neuroprotection [28].

Randomized Controlled Trials of Antipsychotics

Olanzapine ($n = 31$) and placebo ($n = 29$) were compared in a double-blind RCT [25]. Although the 1-year transition rate was much lower in the olanzapine group

(16.1% vs. 37.9%), results from post-hoc analysis remained at statistical trend level only. Yet, the small sample size reduced statistical power considerably. Interestingly, all transitions in the verum group emerged during the first 4 weeks, which may indicate a delayed pharmacological effect. The number needed to treat (NNT) was 4.5, which is considerably lower than, for example, the NNT of 14 shown for prevention of stroke or death by aspirin [29]. Extrapyramidal symptoms did not differ between groups, but weight gain was statistically and clinically significant in the treatment group, a well known problem with olanzapine and a tremendous disadvantage, particularly for indicated prevention. The 2-year follow-up results were inconclusive, as the sample size decreased considerably.

An RCT within the German Research Network on Schizophrenia investigated amisulpride plus "needs-based intervention (NBI)" ($n = 65$) vs. NBI ($n = 59$) [30]. Based on the German clinical staging approach, which differentiates between an early and a late risk syndrome [31, 32] (see Volume II, Chapter 9 for details), participants with a "late-state" condition, i.e., with either APS or BLIPS or both, were included. Preliminary results showed a significantly lower 6-month transition rate in the amilsulpride compared to the control group. Conclusions, however, are limited by the open-label design of the study whose results require confirmation in a double-blind trial.

Another RCT evaluated the effects of "specific preventive intervention (SPI)" ($n = 31$), a combination of risperidone, cognitive-behavioral therapy (CBT) and NBI, in comparison to NBI ($n = 28$) [22]. Raters of intake and transition criteria as well as other measures but not clinicians or participants of the study were blind to the respective condition. The transition rate of the NBI group was significantly higher than that of the SPI group (35.7% vs. 9.7%) after the 6-month intervention period. A difference in transition rate, however, was no longer observable after the subsequent 6-month observation period, during which SPI transition rate doubled, while the NBI transition rate remained stable; NNT was 4. Unfortunately, the study did not allow disentangling the effects of risperidone and CBT. Yet, as full adherence to risperidone was still associated with a significantly lower transition rate in comparison to NBI, the pharmacological part of the SPI condition indeed appeared to be associated with a preventive effect, persisting after treatment cessation. However, more than half of the sample had not been compliant with risperidone; thus, unexplored moderating factors may have mediated compliance effects on transition rates. No relevant side effects were reported, yet no standardized safety assessments had been employed.

As regards long-term effects on average 46 months past baseline, the transition rate was 41.2% in the NBI group (7 of 17 subjects) and 45.8% in the SPI group (11 of 24 subjects), with one transited person having committed suicide during the follow-up period [23]. Though the transition rate in the SPI subsample that had been fully compliant with risperidone during the intervention period remained lower than in the partial or non-compliant subgroup, there were no significant differences in transition rates when compliance with risperidone was taken into account. Yet, the small size (69.5% of the original sample) might have contributed to this lack of significance.

Naturalistic Treatment Study of Antipsychotics and Antidepressants

A naturalistic, nonrandomized observational study followed the effects of antidepressants and second-generation antipsychotics (SGA) up to 5.5 years in adolescents with APS [27]. Medication was prescribed based on independent clinicians' impression of patients' needs. No transition emerged in the group treated with various types of antidepressants ($n = 25$), but 43% in the group treated with SGA ($n = 28$), either alone or in combination with antidepressants. Yet 92% of the converted patients had been noncompliant with SGA, stopping intake up to 20 months before transition. Further, the only compliant converter of the SAG group later turned out to be clozapine resistant (C.U. Correll, congress presentation). Thus, at the time of transition, no active neuroleptic effect can be assumed for any patient of the SAG sample with a transition to psychosis. Nevertheless, both groups had manifested an almost equal decrease of paranoid ideations, unusual thought content and unusual perceptual experiences; yet, grandiose ideas and conceptual disorganization hardly improved in either group [27].

Except for conceptual disorganization, which had been significantly more severe in the SGA compared to the antidepressants group, baseline assessments were not different, but 42.9% of the SGA group had already been treated with antipsychotics before, which may have mitigated initial positive scores. Thus, risk of transition may have been considerably lower in the antidepressant group from the start. In addition, only the minority of the sample received a monotherapy; 57% of the SAG group was also prescribed antidepressants [27]. Hence, this study does not allow any conclusion about differential preventive medication effects. Furthermore, with no report on side effects and with regard to the at least somewhat different baseline conditions, tolerability of medication cannot be estimated.

Despite these methodological limitations, the authors reasoned that continued antidepressant treatment may have had a neuroprotective effect or may have unspecifically reduced stress levels. They also concluded by a recent, subsequent file audit [33] that these and other aspects, such as potential positive effects on negative symptoms, would make antidepressants a very interesting candidate for prevention; yet, to prove this, RCT were warranted. In the discussion about SAG and antidepressants, however, it should be kept in mind that both SGA and antidepressants can produce unwanted effects, particularly in adolescents [34–36]. These potential negative effects are one of the most important issues in prevention of psychosis, as even in the long-term, at least 20% of people have to be assumed as falsely classified as being at risk for psychosis and, consequently, would unnecessarily be exposed to a preventive intervention [37].

Neuroprotective Treatment Trials

Omega-3 polyunsaturated fatty acids (PUFA) are a different, potentially neuroprotective approach [28]. In a double-blind RCT comprising a 12-week intervention with either omega-3 PUFA ($n = 41$) or placebo ($n = 40$) that was followed by a 40-week monitoring period, a transition rate of 4.9% emerged in the verum

condition and of 27.5% in the placebo condition ($p = 0.007$); NNT was 4. Side-effects were not significantly different. A recently started multi-center study will test these findings [38].

Two more studies of neuroprotective intervention in at-risk states are currently awaiting full publication. Glycine, an N-methyl-*d*-aspartate-receptor agonist was evaluated in a small open 8-week pilot trial. In absence of any transitions, significant improvement of different psychopathological domains was reported [39]. Further, in an open 3-month proof-of-concept study, hippocampal T2 relaxation time was significantly reduced in a small UHR group treated with low-dose lithium (450 mg/day), suggesting a protection of hippocampal microstructure [40, 41]. This is the first study providing imaging data on neuroprotective effects in at-risk subjects. However, the clinical and functional consequences of such potential neuroprotective effects still need further exploration.

Prevention Studies Focusing on Psychotherapy

Another approach to an early, preventive intervention, which is generally considered safe in terms of side effects, is psychotherapy. In light of the vulnerability-stress-coping model [42], a general preventive effect of CBT mediated by an increase of protective factors and a decrease of stress factors seems reasonable to assume. This is supported by findings demonstrating that the majority of UHR individuals suffer from different "co-morbid" conditions, especially affective and anxiety disorders [43, 44]. Furthermore, potential effects of cognitive therapy (CT) on positive symptoms [45] are assumed to be even more pronounced, when delusions and hallucinations are only present in an attenuated form and insight is still retained.

Morrison and colleagues evaluated the preventive effects of 6-month CT ($n = 37$; post-hoc exclusion of 2 subjects from final analyses for transition dating prior to baseline) in comparison to a treatment-as-usual (TAU) condition ($n = 23$) [46, 47]. Subjects had to be neuroleptic-naïve at inclusion; yet following study intake, study-independent prescription of antipsychotics was not restricted. Primary outcome measure was transition rate, with symptomatic thresholds operationalized and assessed in a non-blinded manner by the PANSS [48] (see also Volume II, chapter 9 for details). Secondary measures of transition were "DSM-IV diagnoses of a psychotic disorder", based on case vignettes presented to a psychiatrist blind to treatment condition, and "prescription of antipsychotic drugs". In terms of the primary outcome measure and disregarding drop-outs, the 1-year transition rate was 22% in the TAU and 6% in the CT group after the exclusion of 2 already psychotic (see above) participants from analyses. The NNT was 6. Forty-seven percent of the originally analyzed sample ($N = 27$) could be followed up for 3 years [46]. At this, only the secondary outcome criterion "prescription of antipsychotic drugs" still yielded a result significantly in favor of CT; yet alike in other long-term follow-ups [23, 25], the

followed-up sample was only small. In an exploratory approach, controlling for different covariates specifically targeted by CT, i.e., "uncontrollability of unwanted thoughts" and "fear of rejection and criticism", this favorable result could also be repeated for the primary outcome definition using PANSS scores.

However, alike in most pharmacological studies, methodological flaws also complicate drawing conclusions from this trial. However, the results of 4 methodologically sound studies, either ongoing [49–51] or in preparation for publication of results [52], will be very informative with regard to the differential and mixed efficacy of pharmacotherapy and psychotherapy.

A second psychotherapeutic RCT within the German Research Network on Schizophrenia focused on the early state mainly defined by cognitive-perceptive basic symptoms [53] (see Volume II, chapter 9 for details) according to the German clinical staging model [31, 32]. In an open study with a 12-month treatment phase, effects of CBT ($n = 63$) were compared to supportive counseling ($n = 62$). At 24-month follow-up, transition rate to either frank psychosis or a late at-risk state with APS and/or BLIPS was significantly lower in the CBT condition [54, 55].

Treatment Approaches

Clinical syndromes defined by current at-risk criteria are commonly accompanied by several psychopathological, cognitive and functional complaints and lead to help-seeking behavior [56]. Thus, it has been suggested to consider this group not only as at-risk, but also as already ill [56]. In line with this notion, the current proposal for the DSM-V includes a new "Attenuated Psychotic Symptoms Syndrome" [57] (see Volume II, chapter 9 for details). Thus, beyond prevention, treatment matters, too. Olanzapine had a favorable effect on positive symptoms from week 8 to 28; however, weight gain was already a significant problem after the first 8 weeks [25, 58]. Within 12 weeks, amisulpride treated patients showed a significant improvement of attenuated and full-blown psychotic symptoms as well as of basic, depressive and negative symptoms and of global functioning [30]. Elevation of prolactin was the most important side effect indicating the necessity of an intensified monitoring and special caution in adolescents and young adults. Improvement of different domains of at-risk symptoms were also reported from a pilot study investigating aripiprazole over 8 weeks ($n = 15$); the most important adverse event was akathisia [59]. The preventive capabilities of aripiprazole will be further investigated in a recently started German multicenter trial [51]. Omega-3 PUFA showed a positive effect also on the symptomatic level, i.e., all PANSS scores at 12 weeks, 6 and 12 months as well as Global Assessment of Functioning scores [28]. Noteworthy are also results of a 9-month psychoeducative multifamily group treatment of UHR subjects, which led to a wide range of significant psychopathological and functional improvements [60]. This approach was conceptually supported by another study indicating an association between family problem solving style and course of illness in UHR patients [61].

Conclusions and Future Directions

An evaluation of available studies is often done under the presumption that an intervention can only be regarded as successful when its effects remain after cessation of the treatment condition. Thus, a successful intervention with long-term effect would have to override the impact of a complex interplay of genetic, epigenetic, neurodevelopmental and psychosocial factors, starting with conception and determining the risk of and progression to psychosis. Hence, current concepts of an effective preventive measure in terms of rather time-limited interventions need reconsideration. As yet, most preventive studies of limited intervention periods have mainly evidenced a successful delay rather than a prevention of psychosis. In somatic disorders with longstanding risk conditions, however, long-term rather than short-term intervention is a common strategy, e.g., in the prevention of stroke [62]. As implied by the concept of indicated prevention, however, this would certainly require treatment strategies with a very favorable cost–benefit ratio for at-risk individuals. Today, the results of the Omega-3 PUFA study are the only observations indicating that the effects of short-term treatment may be maintained for some time after cessation. Though a long-term effect of a well-tolerated substance would be most desired and a therapeutic breakthrough, these first results still have to be confirmed and extended, particularly with regard to truly long-term effects spanning years. Moreover, it will be necessary to investigate, whether such preventive treatment is also efficient in adults past the main years of brain development.

Further, it seems to doubt that one type of intervention will be able to equally serve the prevention of the whole spectrum of mental conditions subsumed under the term "schizophrenia" or, even broader, "psychosis". All the more that the impact of psychosocial and biological conditions on the development of the psychotic condition probably differs between various types of psychotic disorders and that it is as yet unclear, if current at-risk criteria delineate exclusively a risk of psychosis or also an increased risk of other severe mental disorders, e.g., bipolar disorders. Moreover, the encouraging results of the Omega-3 PUFA trial in at-risk patients have yet another very important implication. They have demonstrated that focusing primarily on interventions, which have been shown to work in frank psychosis, may be a too narrow and misleading approach in the prevention of psychoses. If functional and even structural changes of the brain are indeed an integral part of the process leading to frank psychosis [63–66], at least of those of the schizophrenia-spectrum, it can well be assumed that very early stages of the disease might still be responsive to *preventive* interventions, which fail to be effective as a *curative* intervention in later, acute stages when brain changes are already more pronounced. Thus, it will be most important to intensify basic research efforts in these early stages and to develop new special early intervention approaches from these findings.

Furthermore, recent observations indicate that at least the temporal variance of risk estimation by UHR criteria is broader than originally expected (see also Volume II, chapter 28 for details). Therefore, improved enrichment strategies or clinical staging algorithms that will allow a more individualized risk classification or stratification have to be developed to increase the homogeneity of individual risk

levels in study samples that might be a necessary precondition for conclusive prevention trials. Further, a risk stratification approach will allow adaptation of early interventions to the actual individual risk and concomitant needs of different at-risk groups [67, 68]. However, even once preventive intervention strategies will have proven their efficacy in studies, which will mainly be carried out in at-risk samples seeking help in specialized services, the next future challenge will be to prove the effectiveness of an early intervention at epidemiological level, i.e., with regard to all subjects at increased risk of developing psychosis and not only the subsample of those seeking help early.

To conclude, although the first 15 years of early detection and intervention research in psychoses have already produced encouraging results, much remains to be done before evidence-based intervention guidelines can be developed and implemented into clinical settings.

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Chapter 5
Early Improvement and Its Predictive Validity in First-Episode Schizophrenia Patients

Michael Riedel, Florian Seemüller, Richard Musil, Ilja Spellmann, Hans-Jürgen Möller, and Rebecca Schennach-Wolff

Abstract Despite the ongoing study reports finding early treatment improvement in schizophrenia to be a robust marker of subsequent outcome, research in patients suffering from their first-episode of schizophrenia (FES) has just recently been started. Latest literature reports and newest developments are summarized pointing out the need for future research in terms of early response in FES patients. Data on clinical as well as biological and functional study results are presented and discussed suggesting that early improvement is a significant predictor of subsequent short- as well as long-term outcome in FES patients. The difficulty of the use of different and arbitrarily chosen definitions of early improvement is furthermore addressed and latest study results are shown proposing a systematically analysed early improvement definition for FES patients. Finally, clinical consequences of the identification of early improver and early non-improver are addressed. Today, no clear guidance can be provided regarding the treatment actions that should be taken in early non-improver. Only post-hoc analyses in FES patients are available questioning the study's conclusions suggesting a change of the antipsychotic rather than a "staying on"-strategy. Future studies are warranted to find a consensus understanding of early improvement and especially to develop treatment strategies for patients not achieving early improvement. Given that the first episode of schizophrenia is a critically and very important time-point in terms of the future course of the illness a proper management during this period will favourably influence the long-term course and outcome of the patients. Therefore, further studies on early treatment improvement and its clinical and scientific consequences should be of highest interest and focus for researchers and care providers.

Keywords First-episode schizophrenia · Early improvement · Predictive validity · Outcome

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Abbreviations

BPRS	Brief psychotic rating scale
FES	First-episode schizophrenia
PANSS	Positive and negative syndrome scale

Introduction

Treatment guidelines in schizophrenia have for long recommended to monitor patients' treatment response for at least 4 weeks before increasing or changing medications [1]. Even though this "delayed-onset" hypothesis was questioned already in the 1980s [2], interest in testing this hypothesis was only recently rekindled. Two meta-analyses performed by Agid et al. [3] and Leucht et al. [4] found a substantial amount of the antipsychotic effect to occur during the first weeks of treatment confirming the "early-onset" hypothesis.

Recent studies indicated that, according to the "early-onset hypothesis" of antipsychotic drug action [4], early medication non-improvement is a stable predictor of a subsequent lack of response in schizophrenic patients [5–7]. Identifying early antipsychotic treatment improvement could prevent unnecessary persistence with ineffectual compounds, diminish the risk of adverse events, decrease duration of hospitalisation and reduce illness burden and costs [6]. This seems especially important in patients suffering from a first-episode of schizophrenia, as it is a critically important time point for the future course of the illness with the chance that proper management during this period will favourably influence the long-term trajectory of outcome [8]. The first-episode of schizophrenia illness is considerably important for mostly young patients suffer it and illness based problems might adversely affect schooling or interfere with social relationships and the personal development [9].

Despite the importance of identifying early treatment improvement in FES only a limited number of trials have been performed on this topic so far. Emsley et al. investigated antipsychotic treatment response in FES patients and found time to antipsychotic response to vary widely suggesting that in FES longer treatment trials may be necessary [10]. Crespo-Facorro et al. analysed 172 patients regarding their acute treatment response and stated that the identification of non-responders is the first step to optimise therapeutic effort [11]. Interestingly, although both first- and second-generation antipsychotics have demonstrated a similar likelihood to achieve a favorable response during early phases of schizophrenia [12, 13] data on early improvement is furthermore standing out. This is even more surprising given the ongoing debate about a potential benefit of second- over first-generation antipsychotics for this might result in specific treatment actions.

A major problem of research in this field besides the low number of studies examining early improvement in FES patients is the application of arbitrarily chosen definitions of early improvement hindering cross-comparison of study results and

slowing down the specific development of treatment strategies. Besides, it is unclear what to do with patients not achieving an early improvement to antipsychotic treatment. Three different treatment options are available in early non-improvers: (1) Changing the antipsychotic that was applied or (2) Increasing the dosage of the primarily chosen antipsychotic or (3) Following the "wait and see" strategy with no clear recommendation today due to the lack of prospective randomized trials.

Just recently, first study reports have been published trying to overcome past limitations and to shed light on current vagueness. Therefore, this chapter will provide an overview on early improvement and its importance in first-episode patients with focus on the latest developments and recommendations.

Early Improvement in FES Patients and Its Predictive Validity Regarding Outcome

Clinical Data

General Aspects on Early Improvement in FES Patients

It is well known that FES patients will more often respond to antipsychotic treatment and feature a favorable treatment outcome as compared to patients with multiple episodes [14]. Emsley et al. were among the first to examine an early response to treatment as potential predictor of subsequent outcome [15]. In a 2-year-follow-up study the authors analysed 57 patients with first-episode psychosis incorporating various demographic, baseline clinical, and early response variables to predict remission/non-remission. The patients' symptom improvement patterns over time were furthermore assessed. The prediction model correctly predicting remission in 89% of the cases and correctly predicting non-remission in 86% of the patients revealed that response in week 6 was among the significant predictors of remission after 2 years [15]. In a similar analysis Emsley et al. examined 462 patients with their first-episode of schizophrenia and followed them up for 4 years. Again, the authors were able to show that response to treatment within the first 6 weeks of treatment was among the two strongest predictors of remission [16]. The other significant predictor identified was the duration of untreated psychosis. Interestingly, besides showing that an early improvement within the first six treatment weeks was a significant predictor of remission Emsley et al. also reported that patients in remission received a lower mean daily dose of antipsychotic medication [16]. This suggests that these patients generally seem to have a more favorable course of the illness indicating that early improvement might be a marker for a better long-term outcome.

Interestingly, not only early symptom improvement but also early improvement in subjective well-being has been examined in first-episode schizophrenia patients. DeHaan et al. analysed 110 admitted patients suffering from a first episode of schizophrenia and examined an early improvement of the patients' subjective well-being and early symptomatic improvement and the association to

enduring symptomatic remission during 5 years of follow-up [17]. Early symptomatic improvement was found to be related to reaching symptomatic remission at week 6 and after 6 months, however this relationship did not hold when applying stringent remission criteria, namely continued symptomatic remission for 4½ years [17]. Patients with enduring symptomatic remission had a higher mean improvement of their subjective well-being during early treatment compared to patients without enduring symptomatic remission suggesting that early improvement of subjective well-being is related to enduring symptomatic remission in FES patients.

Antipsychotic Treatment and Early Improvement

Schennach-Wolff et al. examined early improvement in 188 first-episode patients within a randomized double-blind trial comparing treatment with risperidone and haloperidol [18]. They did not find a significant difference regarding response and remission rates at discharge when comparing patients treated with risperidone and haloperidol. Also, no significant difference was reported in terms of early improver rates as well as concerning predictive validity of early improvement comparing patients receiving risperidone or haloperidol [18]. These results somewhat resemble current data deriving from clinical as well as double-blind controlled trials finding almost no significant differences in efficacy comparing a first- and a second-generation antipsychotic [13, 19, 20].

A Standardized Definition of Early Improvement in FES Patients

Differing definitions of early improvement such as a score reduction in the *Brief Psychotic Rating Scale* (BPRS) of 4 points at week 1 to best predict response at week 4 [6] or a <20 or >20% total score improvement in the *Positive and Negative Syndrome Scale* (PANSS) at week 2 to best predict subsequent response [21, 22] point out current inconsistencies in the definition of early improvement. Besides, some proposed cut-offs were arbitrarily chosen emphasizing the need for a systematic analysis.

Consequently, given the importance of an early and adequate symptom control in FES patients a systematic analysis was performed to identify the best fitting definition to predict subsequent outcome using sensitivity/specificity analyses. Based on current literature reports the patients' psychopathological improvement at treatment week 2 was examined regarding its predictive validity in terms of achieving subsequent response and remission (Fig. 5.1).

Schennach-Wolff et al. reported that at week 2 a 46% improvement in the PANSS total score was found to best predict response and a 50% improvement to best predict remission. Despite the common use of such sensitivity/specificity ROC-analyses the authors also discussed critical aspects of this statistical procedure. The main problem was found to be the fact that the results can often not be generalized because they depend heavily on the patient sample that has been examined. Even small changes in the data can change the resulting cut-off enormously. The authors believe that this is one reason for the diversity of the different proposed

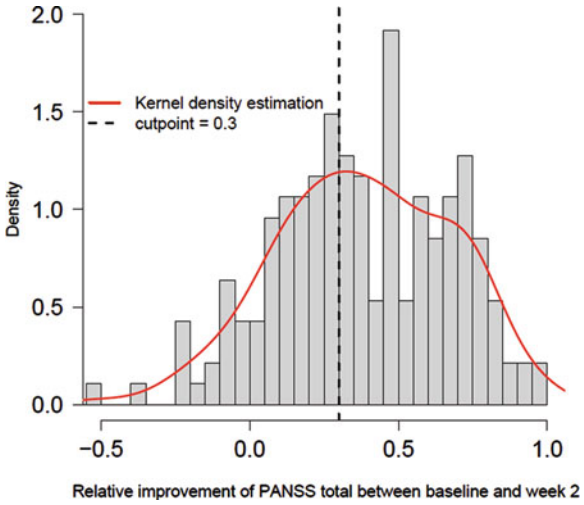

Fig. 5.1 Histogram of 188 first-episode schizophrenia patients and their psychopathological improvement from baseline to treatment week 2. The patients were treated with risperidone ($N = 93$) or haloperidol ($N = 95$). Each balk represents the relative number of patients whose psychopathological improvement is located in the respective interval. One conclusion that can be drawn from this figure is that more patients were early improver than early non-improver underlining the favorbale response to treatment in FES patients already early in the beginning of the treatment

definitions of early improvement. In this context it should be noted that incorrect calculations of the PANSS might have further contributed to the inconsistent data in this respect [23]. In order to adjust for the dependency of the underlying sample when performing sensitivity/specificity ROC-analyses the authors computed bootstrap intervals by using resample methods [24] with confidence intervals as a result which by definition cover the true cut-off for the population of FES patients with the probability of 95%. A confidence interval of a 26–60% PANSS total improvement to predict response and a confidence interval of a 28–61% improvement to predict remission were found to be the best fitting cut-off definitions. Due to the heavily overlapping intervals the authors suggested to use a similar cut-off definition to predict response and remission in FES patients. The authors found both cut-off intervals impractical suggesting a rounded off interval of a 30–60% PANSS total score improvement at treatment week 2 as best fitting definition. Interestingly, Schennach-Wolff et al. found 23% of the patients in their study to achieve a 60% PANSS total score improvement at week 2 concurrently being responder at week 8 and 22% of the patients being remitter suggesting that a 60% improvement at week 2 to predict subsequent response and remission is not unrealistic in FES. This cut-off should be applied and re-evaluated in future studies. This standardized early improvement definition should, however, increase the generalizability of treatment results in this field of research and with this enhance the understanding of early improvement in this patient population.

Functional, Biological and Experimental Data

EEG Data

Specific pathobiological processes mediate the time to antipsychotic treatment response which is why experimental and functional studies can considerably contribute to the understanding of the phenomenon of an early improvement in treatment. In an EEG study Merlo et al. searched for differences in the EEG of FES drug-naïve [25]. The patients were compared using two different patient groups namely patients with a clinically meaningful improvement of their psychopathology (reduction of more than 30%) after 7 days of treatment (= early responder) and those patients showing this improvement after 28 days (= non-early-responder). Merlo et al. were able to detect significant differences between these patient groups (early responder versus non-early-responder) in the alpha2 and beta2 frequency band with lower alpha2 and beta2 power in the early responder [25]. These results suggest differences in brain physiology between early and non-early improver helping to predict response patterns. Besides, such results underline the concepts proposed by older psychiatrists, such as Emil Kraepelin and Eugen Bleuler, who suggested that schizophrenia illness is a phenotype of different pathophysiological processes [26].

Imaging Data

Despite the clinical data on the predictive power of early improvement in terms of subsequent outcome the corresponding regional neuronal changes taking place in the early stages of antipsychotic treatment are still not well understood. However, several studies using magnetic resonance imaging or positron emission tomography have tried to add information to the growing body of research on early improvement to antipsychotic treatment in patients with first-episode schizophrenia. Garner et al. for example examined early improvement to antipsychotic treatment in 42 drug-naïve patients suffering from their first episode of schizophrenia and focused on the patients' response to treatment and the pituitary volume [27]. The hypothesis of a possible association between early treatment improvement and the pituitary volume was based on literature reports finding the onset of schizophrenia and related disorders being associated with increased levels of stress and hyper-activation of the hypothalamic-pituitary-adrenal axis. The patients in the study by Garner et al. were treated with quetiapine fumarate. As hypothesized the authors found a significant association between the pituitary volume and the degree of psychopathological improvement namely that patients with a larger pituitary volume showed less overall improvement.

Another recently published study, however not specifically focussing on first-episode patients, analysed regional brain changes and their correlation to treatment response in 29 schizophrenia patients using positron emission tomography [28]. They evaluated the time course of regional cerebral blood flow patterns generated by a first- (haloperidol) and a second-generation (olanzapine) antipsychotic and

observed regional cerebral blood flow pattern changes that were common to both antipsychotics implicating cortico-subcortical and limbic neuronal changes related to an early (ventral striatum, hippocampus) and consolidated response. After the first treatment week a greater regional cerebral blood flow pattern increase in the ventral striatum and a greater decrease in the hippocampus were associated with good response.

Genetic Data

Evidence from different studies suggested that the individual variability in antipsychotic treatment response might be genetically determined. Variations in several serotonin transporter gene polymorphisms have long been associated with antipsychotic response among chronic schizophrenia patients, their implication in early response among first-episode patients has just recently been examined. Vázquez-Bourgon et al. genotyped two polymorphisms in the serotonin transporter (5-HTT gene, a 44 bp insertion/deletion in the promoter region and the functional polymorphism rs25531) in a sample of 147 drug-naïve patients experiencing a first episode of psychosis [29]. Different psychopathological rating scales were applied to examine early response to treatment within the first 6 weeks of treatment (defined as a 40% improvement on the BPRS). No clear association was found between the rs25531 variant and treatment response. However, significant associations were detected between 5-HTT-LPR (Serotonin *T*ransporter *L*inked *P*romotor *R*egion) variants and early negative symptom improvement among the FES patients suggesting a minor contribution to antipsychotic drug response of genetic alterations in the 5-HTT gene [29].

Reynolds et al. genotyped D2, D3 and 5-HTC receptor polymorphisms with early symptom response (defined as 50% change in the PANSS total score at week 10) in 117 FES patients following a 10-week antipsychotic treatment, primarily with risperidone or chlorpromazine [30]. The D2 polymorphism was found not to be significantly associated with baseline levels or changes in the total score of the PANSS. The D3 genotype was associated with changes in the PANSS total score. The 5-HTC2 promoter polymorphism was also associated with improvement in the PANSS, but reflecting effects on negative and general, but not positive, symptom scores [30]. This polymorphism was not associated with the PANSS score on admission.

These results should be discussed with caution as they need to be replicated in larger and independent samples given that treatment response in schizophrenia is thought to be a complex and multifactorial event and cannot be explained as an effect of one single genetic variation [30]. Another limitation is the fact that environmental factors were not considered in previously reported studies. However ongoing studies genotyping other candidate genes examining combined treatment effects (genes and environment) might present more evidence for a genetic cause of an early response to treatment.

Data Considering the Long-Term Course of the Illness

Given the importance of early improvement to antipsychotic treatment in terms of course and outcome of the illness it is very surprising that only few studies evaluated early improvement regarding its predictive value considering long-term treatment especially in FES patients. Especially on the background of the hypothesis that early response is a marker of an overall benign illness course. Lambert et al. examined early response (defined as achieving symptomatic and functional remission as well as adequate subjective well-being after 3 months) and its predictive value for remission and recovery within a 3-year trial and found response within the first 3 months to be one of the two best predictors [31]. And as mentioned before Emsley et al. assessed remission within a 4 year trial confirming early response to be significantly predictive for subsequent remission [16].

As already discussed, one major problem hindering research in this field is that arbitrarily chosen definitions were applied which have not been examined in long-term studies. It is unclear if the most often used definition of an at least 20% PANSS total score improvement from baseline to week 2 [32] is adequate enough to identify early improver regarding long-term treatment. The same questions raises regarding the newly proposed standardized definition of early improvement of an at least 30% improvement for this cut-off was evaluated using an 8-week short-term study. In order to predict the long-term course of schizophrenia it might be more appropriate to use a more stringent cut-off possibly examining early improvement later than the second treatment week. Besides, both currently proposed and used cut-offs stand against established treatment guidelines recommending a change of treatment not before the sixth treatment week [33].

Just recently, Schennach-Wolff et al. evaluated the predictive validity of early improvement within a 1-year follow-up trial in FES patients. The authors followed two different study aims: 1. To identify the optimal assessment time-point of early improvement regarding long-term treatment and 2. To identify the best cut-off of early improvement when applying the definition within a long-term study. This newly developed cut-off was then compared to the currently proposed early improvement definition (20% improvement by week 2). They examined 132 patients using receiver operator characteristic analyses to identify the predictive validity of the patients' psychopathological improvement of treatment week 1 to week 8 regarding response at week 52. Response at week 52 was defined as a 50% PANSS total score improvement. Interestingly, a considerable number of patients were identified to achieve the response criterion of a 50% PANSS total score improvement already in the first treatment weeks. The Youden-Index (maximum of sensitivity and specificity) was used to compare the newly developed and the commonly used early improvement definition (Fig. 5.2).

Starting with week 6 the authors detected a reasonable validity to predict response at week 52 (AUC = 0.721). Therefore, the best fitting cut-off was then analyzed for week 6 finding a 51.6% PANSS total score improvement to best predict response at week 52. Regarding the comparison of the newly developed and the currently used early improvement definition the Youden-Index was higher applying

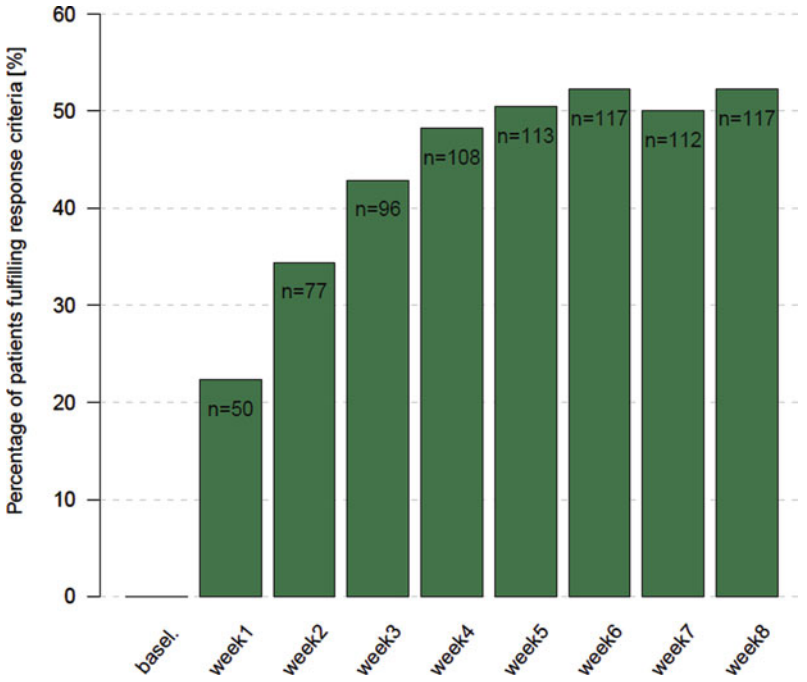

Fig. 5.2 One hundred and thiry two patients and their response to treatment were examined within a randomized controlled trial comparing risperidone and haloperidol. This figure shows the number of patients achieving the response criterion for the first time (≥50% PANSS total score reduction) during the acute treatment phase (treatment weeks 1–8)

the newly developed early improvement cut-off featuring higher specificity compared to the commonly used early improvement definition of a 20% improvement at week 2. Schennach-Wolff et al. concluded that regarding long-term treatment it might be more appropriate to base predictions on the patient's 1-year-response not before 6 weeks of treatment. They question the applicability of the currently used early improvement definition and suggest a critical re-evaluation regarding its use in long-term treatment.

Interestingly, in another post-hoc analysis Derks et al. tried to answer a similar question namely whether or not patients should be switched to a different antipsychotic drug after 2, 4, or 6 weeks of nonresponse. The data were derived from the European First-Episode Schizophrenia Trial (EUFEST) [34]. The authors performed logistic regression analyses to test whether the prediction of remission after 1 year would be improved by including assessments obtained 4 or 6 weeks from treatment initiation compared with a prediction based on baseline and 2-week measures only. When predicting remission using baseline and 2-week assessments the authors were able to correctly predict remission in 61% of the patients compared to 63 and 68% when including the 4- and 6-week assessments respectively. Derks et al. concluded that with their analyses they confirmed previous findings that 2-week measures of

response are associated with remission [34]. However, the prediction of remission based on the 2-weeks assessments was poor but improved when 4- and 6-week measures were included. These results suggest that switching should not occur before 6 weeks of treatment. But, because the prediction accuracy was only improved by 5% comparing measures of week 4 and week 6 the authors discussed their results cautiously in terms of their clinical relevance.

Future studies with a prospective design are warranted to replicate these findings in order to propose the best fitting early improvement definition and time point for the clinical and scientific use enhancing comparability and generalizability of the results. This is especially important in terms of the clinical consequences drawn from such analyses. Because consequently, when proposing the second treatment week to evaluate early improvement one would think that in non-early-improvers the treatment should be adopted or changed to improve their outcome. However, if the sixth week of treatment is more adequate to predict subsequent outcome the patient's response should not be evaluated before that time-point. This dilemma highlights the need of a standardized and consensus understanding of early improvement also in long-term treatment. Given the fact that schizophrenia is a life-long illness the need of a long-term treatment should not be lost out of the focus.

What Actions Should We Take in Patients Not Achieving Early Improvement?

As previously discussed, the evaluation of early improvement results in specific treatment actions. However, in addition to the fact that it is still unclear when to examine early improvement and how much psychopathological improvement is necessary to become early improver it is also very vague what to do with patients not achieving early improvement. Today, no prospective study has been performed in FES patients so far comparing different treatment approaches in patients not becoming early treatment improver. Especially the question of whether or not a change of treatment might improve the patient's long-term outcome or if an increase of the primarily applied antipsychotic might be adequate enough in early non-improver remains unanswered.

A post-hoc analysis of FES patients examined within a randomized controlled trial already described before tried to identify whether specific treatment approaches might have led to a psychopathological improvement in non-early improvers (Schennach-Wolff et al., 2010, Should early response be re-defined in long-term treatment?, "unpublished"). Despite the randomized and controlled design of the study flexible dosing of the antipsychotics (risperidone and haloperidol) was possible according the clinician's judgement. The PANSS total score comparing patients achieving/not achieving the early improvement criterion (an at least 30% PANSS total score improvement by week 2) showed that patients not achieving an early improvement suffered from more psychopathological symptoms from baseline on than early improver (Fig. 5.3).

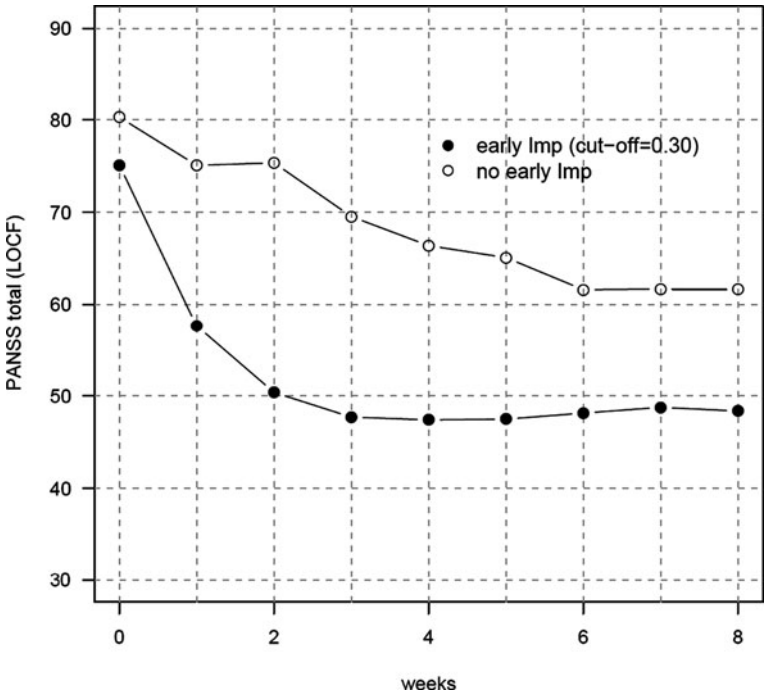

Fig. 5.3 This figure shows the PANSS total score of 188 first-episode schizophrenia treated with either risperidone or haloperidol. The PANSS total score of patients achieving the newly proposed early improvement definition for FES patients (≥30% PANSS total score improvement at week 2) were compared to those patients not achieving this cut-off respectively. This figure is part of the article by Schennach-Wolff et al. [18]

In terms of the treatment applied the authors found it interesting that clinicians treated early non-improvers intuitively with significantly higher doses of risperidone or haloperidol starting in treatment week 2 (Schennach-Wolff et al., 2010, Should early response be re-defined in long-term treatment?, "unpublished") (Fig. 5.4).

But despite receiving significantly more antipsychotic medication early non-improver still achieved response and remission significantly less often. This suggests that a dose-increase might not be sufficient enough, but a change of the antipsychotic compound or the implementation of further treatment strategies might be necessary to assure a satisfying outcome (Schennach-Wolff et al., 2010, Should early response be re-defined in long-term treatment?, "unpublished").

The only prospective study available today examining early improvement as a clinical marker of subsequent response in schizophrenia patients was performed by Kinon et al. and enrolled 628 chronically ill patients diagnosed with schizophrenia or schizoaffective disorder [32]. Even though the authors did not evaluate FES patients the results might also be relevant for the treatment of first-episode patients as they are the only prospective data available. Kinon et al. assessed whether early

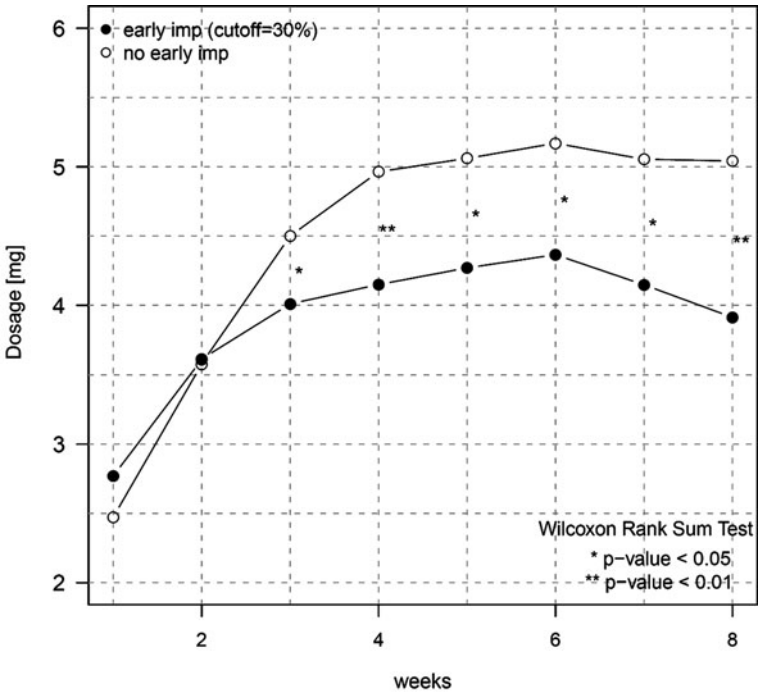

Fig. 5.4 Shows the mean antipsychotic dosage applied in patients achieving/not achieving the proposed early improvement definition for FES patients (≥30% PANSS total score improvement at week 2). Starting with treatment week 2 the patients not achieving an at least 30% PANSS total score improvement received significantly higher dosages of risperidone/haloperidol. This figure is part of the article by Schennach-Wolff et al. [18]

(2 weeks) response to an antipsychotic would predict later (12-week) response and whether "switching" early non-responders to another antipsychotic is a better strategy than "staying" [32]. This was a randomized, double-blind, flexible-dosed, 12-week study. All patients received treatment with risperidone in the beginning. Early improvement was defined as a ≥20% improvement on PANSS total score following 2 weeks of treatment. Early improvers continued on risperidone, whereas early non-responders were randomized to continue on risperidone 2–6 mg/day or switched to olanzapine 10–20 mg/day for 10 additional weeks [32]. Compared with early non-improver risperidone early improver showed significantly greater reduction in the PANSS total score and early improvement/non-improvement was highly predictive of subsequent clinical outcomes. Switching risperidone early non-improver to olanzapine at week 2 resulted in a small but significantly greater reduction in PANSS total score and in depressive symptoms compared to staying on risperidone treatment.

This is the first prospective study showing that a "switching" strategy may lead to greater clinical improvement than staying on a drug for a longer period in some patients and thus prospectively confirmed that early improvement is a robust

predictor of longer-term outcome [32]. However, given the fact that some patients switched to olanzapine experienced changes in safety parameters the switching strategy suggests a balance of risks and benefits when determining appropriate treatment for an individual patient. Keeping study results in mind finding FES patients to be considerably vulnerable to side effects [35] the switching strategy should be critically discussed in this patient population highlighting the need to perform future studies specifically evaluating this aspect in prospective and controlled studies in FES patients.

Conclusions and Future Directions

Early improvement in patients suffering from their first-episode of schizophrenia illness is a significant and stable predictor of subsequent response and remission and is one of the most replicated predictors of schizophrenia research. This was also demonstrated in long-term studies. An at least 30% improvement in the PANSS rating scale within the first two treatment weeks was proposed as standardized definition of early improvement in FES patients to predict outcome at treatment week 8. In terms of long-term outcome it seems more appropriate to base the prediction of subsequent response and remission not before the sixth week of treatment and to define early improvement more stringent, namely as an at least 50% improvement in the PANSS total score. The clinical consequences of non-early improvement are still unclear. Post-hoc analyses in FES patients suggest that an increase of the antipsychotic dosage applied might not be sufficient enough to improve the outcome of early non-improvers. A prospective study in FES patients comparing a change of treatment with the "staying"-strategy is still standing out. Also, future studies need to develop a consensus understanding of what early improvement in FES patients really is and to decide on when and how to evaluate it. Only with a standardized and consensus understanding and evaluation of early improvement can solid clinical consequences be drawn to improve the outcome of FES patients.

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Chapter 6
Antioxidants as a Treatment and Prevention of Tardive Dyskinesia

Vladimir Lerner

Abstract Tardive dyskinesia (TD) is characterized by repetitive, involuntary, purposeless movements of the tongue, lips, face, trunk, and extremities that occur in patients treated with long-term dopaminergic antagonists and following exposure to L-dopa, amphetamine, metoclopramide, cinnarizine, flunarizine and other substances. The term tardive dyskinesia refers to: classical TD (bucco-lingual-masticatory triad), tardive akathisia, tardive dystonia, tardive tremor and other tardive extrapyramidal subsyndromes. The mechanisms of TD remain unclear, although pathophysiologic theories have proposed mechanisms such as dopamine receptor supersensitivity, the degeneration of cholinergic striatal interneurons, γ-aminobutyric acid (GABA) depletion, and an excess of free radicals. Though a wide range of medications for the treatment of TD has been studied, management of this distressful side effect remains a significant problem for patients and a therapeutic conundrum for physicians. According to current concepts, antioxidants such as vitamins and other antioxidative agents may be considered active components of putative therapies because antioxidants inhibit free radical distractive activities. This chapter focuses on evidence from clinical and basic science studies that support the role of antioxidants (vitamins B_6 and E, omega-3, ginkgo biloba, piracetam) as potential neuroprotective compounds and effective medications for the prevention and management of TD.

Keywords Neuroprotection · Vitamin B6 · Vitamin E · Omega-3 · Piracetam · Ginkgo biloba · Schizophrenia · Tardive dyskinesia · Clinical trials

Abbreviations

5-HT	Serotonin
AIMS	Abnormal involuntary movement scale

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BPRS	Brief psychiatric rating scale
CNS	Central nervous system
ESRS	Extrapyramidal symptom rating scale
FGAs	First-generation antipsychotics
GABA	Gamma-aminobutyric acid
IU	International unit
PANSS	Positive and negative syndrome scale
SGAs	Second generation agents
TD	Tardive dyskinesia

Introduction

In 1952, "chlorpromazine", the first anti-psychotic agent for the treatment of psychosis was introduced in psychiatric practice. Soon after, additional neuroleptic drugs extended the armamentarium of treatment for patients suffering from psychotic disorders. After the initiation of neuroleptic treatment, prescribing physicians began to notice the appearance of repetitive, involuntary, uncontrollable movements in some of their patients. At first, clinicians did not relate the involuntary movements to pharmacotherapy since the types of movements and mannerisms revealed are often exhibited by individuals with psychiatric disorders. However, across time, it became evident that movement disorders were drug-induced, and they have since become a growing problem in clinical psychiatry. The side effect was finally recognized in 1964 and was called tardive dyskinesia (TD).

TD is a complex hyperkinetic syndrome characterized by repetitive, choreiform, athetoid or rhythmically involuntary, purposeless movements, such as grimacing, tongue protrusion, lip smacking, puckering and pursing of the lips, and rapid eye blinking, as well as uncontrollable movements in other parts of the body [1–5].

People with schizophrenia and other neuropsychiatric disorders are especially vulnerable to TD after exposure to neuroleptics, anticholinergics, toxins, substances of abuse, and other agents. It is most common in patients with schizophrenia, schizoaffective disorder, or bipolar disorder who have been treated with antipsychotic medication for long periods [6–8].

The prevalence of TD among patients treated with classic neuroleptics for over 1 year, ranges from 3% to as high as 70% (depending on the diagnostic criteria and/or methodology) [1, 8, 9]. The annual incidence in younger adults is 4–5% [1, 4]. Many cases are persistent, often irreversible, and may result in social and physiological impairment. Diagnosis of neuroleptic-induced TD generally requires exposure to neuroleptics for at least 3 months. At least 1 month of exposure is typically required if the patient is 60 years old or more [10].

First generation antipsychotic agents including haloperidol, fluphenazine, trifluoperazine and other similar drugs such as cinnarizine, flunarizine and metoclopramide are known to induce TD. In addition, other pharmacological classes such as anticholinergics, antidepressants, antiepileptic drugs, antihistamines, antimalarials,

antiparkinson agents, anxiolytics, mood stabilizers and others [11] have also been associated with TD.

Although second generation antipsychotic agents (SGAs) have a significantly reduced potential for causing acute and tardive neuroleptic-induced extrapyramidal symptoms including TD [12–14], they may also induce tardive movement disturbances [15–24]. In a recent study, researchers compared the incidence of tardive dyskinesia among patients treated with atypical versus conventional antipsychotics. Contrary to most previous studies, they found a higher incidence of tardive dyskinesia in patients recently exposed to atypical antipsychotic monotherapy that was similar to the rate of TD among patients treated with conventional antipsychotic agents. The authors concluded that despite high penetration of atypical antipsychotics into clinical practice, the incidence and prevalence of tardive dyskinesia appeared relatively unchanged since the 1980s. According to their opinion, clinicians should continue to monitor for tardive dyskinesia, and researchers should continue to pursue efforts to prevent or treat TD [25].

Furthermore, despite the extensive use of SGAs in the majority of western countries, most patients in countries of the third world and up to half in Europe are still treated with classic neuroleptics.

Despite many years of research, and various theories regarding the development of movement disorders the pathogenesis of tardive dyskinesia remains to be elucidated [26]. To date, several neurochemical hypotheses have been proposed for the development of tardive dyskinesia, including dopaminergic hypersensitivity, disturbed balance between dopamine and cholinergic systems, dysfunctions of striatonigral GABAergic neurons and excitotoxicity. Recently, the role of oxidative stress and structural abnormality in the pathophysiology of tardive dyskinesia has gained impetus. Induction of free radicals by neuroleptic drugs leading to oxidative stress and resultant structural abnormality could be the key factor in the pathogenesis of tardive dyskinesia. This hypothesis has been supported by numerous reports that chronic neuroleptic treatment increases free radical production and causes structural damage [27].

TD is a serious side effect and to date no pharmacologic treatment has been proven to be universally or even typically effective in the treatment of TD.

Although a broad spectrum of medications has been investigated in the search for effective treatment of TD, management of this distressful side-effect remains a significant problem for patients and a therapeutic conundrum for physicians [28].

We present cumulative data concerning the use of antioxidants in the treatment of TD.

Piracetam in Treatment of TD

Piracetam (2-oxo-1-pyrrolidone-acetamide) is a nootropic drug structurally related to GABA. The main mode of action of this drug seems to be its beneficial influence on cell metabolism, including that of central neurons. According to several

experimental and clinical studies, piracetam has the potential to preserve, protect and enhance brain synaptic membrane and receptor structure and plasticity, especially under detrimental conditions such as hypoxia, chemical toxicity or impaired cerebral microcirculation [29–32]. However, in a recent review of the effects of piracetam in acute ischemic stroke and the prevention of early death, the author concluded that the piracetam group of patients did not differ from the placebo group [33]. Piracetam increases high-affinity choline uptake and elevates the density of frontal cortex acetylcholine receptors [34, 35]. It also affects glutamate neurotransmission at the micromolar level [31, 36]. In addition, piracetam potentiates potassium-induced release of glutamate from hippocampal nerves [30]. However, the mechanism of action for treating TD remains unknown.

A number of clinical reports have suggested that piracetam may be effective in improving symptoms in a range of movement disorders, including acute neuroleptic-induced extrapyramidal symptoms and TD [37–44]. In these reports, the dose of piracetam used for treating TD varied from 800 to 24,000 mg/day [39, 40, 44]. To date, there has been only one double-blind crossover study performed over 20 years ago using intravenous piracetam in the treatment of TD [39]. Although the findings of this study were impressive, they have not been replicated.

We assessed 40 schizophrenic and schizoaffective patients with TD in a 9-week, double-blind, crossover, placebo-controlled trial [45]. The clinical and demographic characteristics of the patients are presented in Table 6.1.

All study subjects received their usual antipsychotic treatment. Initially, the subjects were randomly assigned to receive either 4 weeks of add-on treatment with either piracetam (4800 mg/day) or placebo. Thereafter, following a washout period of 1 week, they entered the crossover phase of the study for a further 4 weeks. The change in score of the ESRS from baseline to the study endpoint was the primary outcome measure.

The results of the study demonstrate that piracetam appeared to be effective in reducing the symptoms of TD. The average decrease from baseline to endpoint in the Clinical Global Impression (CGI) subscale in patients treated with piracetam was 0.9 points, compared to 0.1 points in the placebo group ($p < 0.004$). The average decrease in the parkinsonism subscale was 8.7 points in patients treated with piracetam, and 0.6 points in those on placebo ($p < 0.001$). The average decrease in the dyskinesia subscale was 3.0 points in the piracetam group in contrast to deterioration in the placebo group – 0.2 points ($p < 0.003$) (Figs. 6.1, 6.2, and 6.3).

Our study supports previous reports [38, 39] that piracetam may be a useful agent in the treatment of drug-induced TD.

Although the mechanism of action of piracetam is not known, we may postulate as to the theoretical possibilities. Since the loss of striatal cholinergic neurons may be a basis for the development of TD [46], one explanation relates to the ability of piracetam to elevate the density of acetylcholine receptors in the brain [34, 35]. Another explanation is derived from the theory that free radicals are neurotoxic and that the antioxidant properties of piracetam [47] may neutralize this damaging effect.

Table 6.1 Demographic data and clinic characteristic of patients at baseline [45]

	Patients ($N = 40$)	Randomization	
		Piracetam ($N = 21$)	Placebo ($N = 19$)
Gender: (N)			
Female	16	7	9
Male	24	14	10
Age (years)			
Mean ± SD:	47.4 ± 11.6	44.9 ± 12.4	50.1 ± 10.2
Range:	24–69	26–69	24–69
Smoker	31	17	14
Nonsmoker	9	4	5
DSM-IV diagnosis:			
Schizophrenia	24	10	14
Schizoaffective Disorder	16	11	5
Duration of illness (years)			
Mean ± SD:	21.4 ± 11.2	22.6 ± 12.3	20.1 ± 10.0
Range:	3–45	3–45	6–39
Duration of TD (years)			
< 3	25	11	13
3–5	8	6	3
>5	7	4	3
ESRS baseline scores ± SD			
Parkinsonism	21.3 ± 10.6	22.8 ± 11.7	19.5 ± 9.2
Dyskinetic	7.8 ± 5.2	8.7 ± 6.4	6.8 ± 3.3
CGI	3.8 ± 0.8	3.8 ± 0.9	3.9 ± 0.8

There were not significant differences between the two groups

Vitamin B_6 (Pyridoxine) in Treatment of TD

The treatment of TD with vitamin B_6 is also not a new approach. In 1978 a small study regarding the use of vitamin B_6 for TD was published in the Journal of Clinical Psychiatry [48]. The authors reported that patients were treated with 1000–1400 mg/day of vitamin B_6. The movement disorders in 4 out of 5 patients improved and the high doses of the vitamin were well tolerated.

Some researchers reported motor disturbances that were observed in vitamin B_6-deficient animals [49, 50]. The rationale for using vitamin B_6 for treating TD is based on the fact that pyridoxyl-5-PO4, derived from dietary pyridoxine, serves as a co-factor in the enzymatic decarboxylation of dopa to dopamine [51] and other metabolic transformations [52, 53]. In the nervous system, pyridoxine dependent enzymes subdivide into two major categories: a) transaminases and b) L-amino acid decarboxylases. Certain of these enzymes are responsible for the production of GABA and others are involved in the synthesis of 5-HT [52] and melatonin [54].

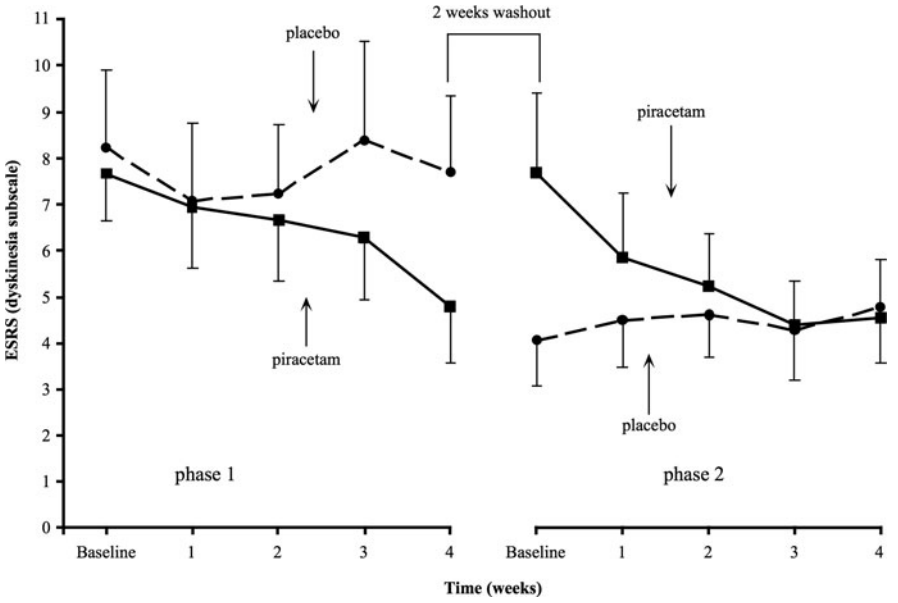

Fig. 6.1 Efficacy of piracetam vs. placebo in schizophrenic patients with TD, dyskinetic subscale ($n = 35$)

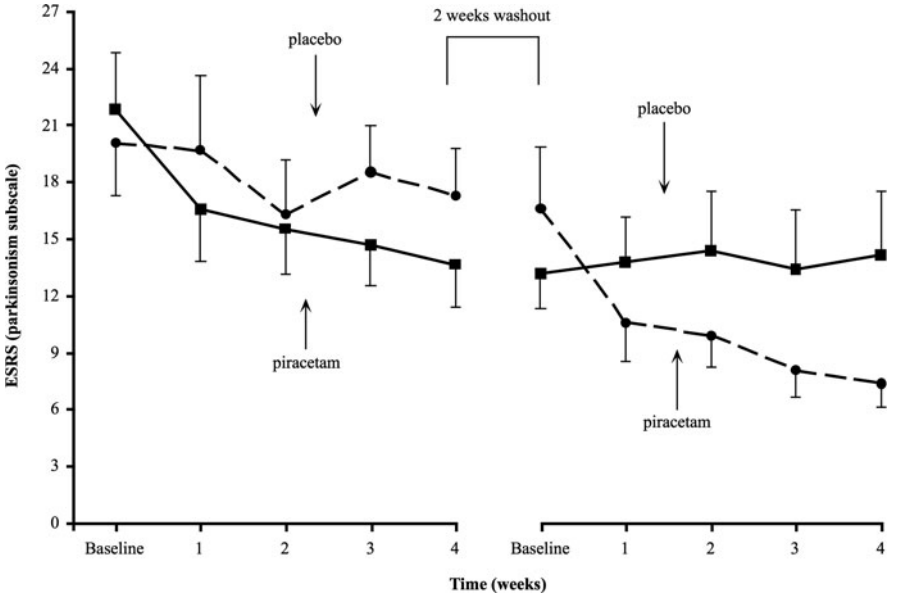

Fig. 6.2 Efficacy of piracetam vs. placebo in schizophrenic patients with TD, parkinsonism subscale ($n = 35$)

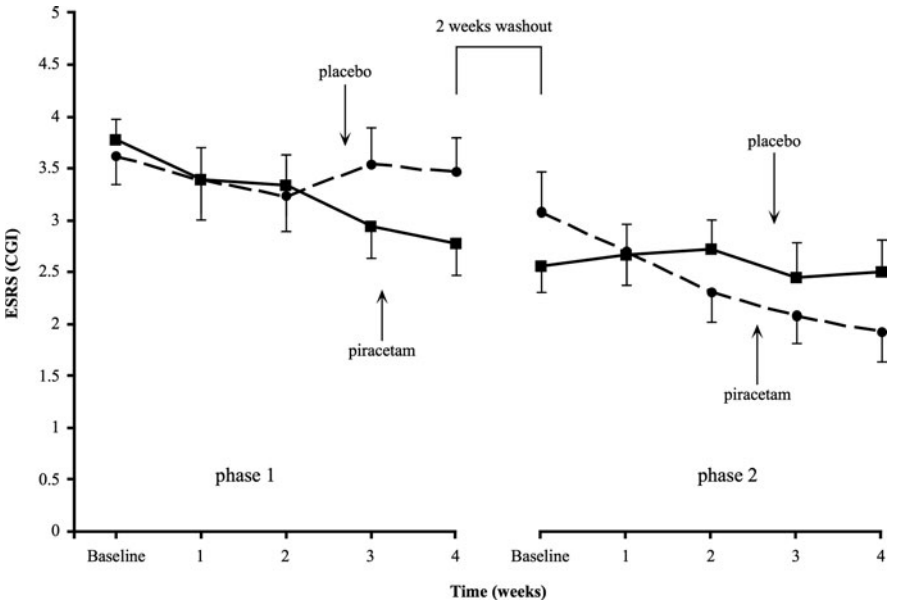

Fig. 6.3 Efficacy of piracetam vs. placebo in schizophrenic patients with TD, CGI subscale ($n = 35$)

On the other hand, vitamin B_6 also takes part in oxidative reactions [55, 56]. Thus it takes part in almost all possible mechanisms associated with the development of this movement disorder. Preliminary evidence of the efficacy of vitamin B_6 in treatment of TD and other involuntary drug-induced movement disorders has been published in several case reports [48, 55, 57–60], open-label trials [61, 62], and randomized, double-blind, placebo controlled trials [63–66]. With one exception [48], the dose of vitamin B_6 was relatively low (range of 100–500 mg daily).

In two double-blind randomized crossover placebo controlled studies our research group evaluated the efficacy of vitamin B_6 in the treatment of TD in different doses – 400 mg/day [65] and 1200 mg/day [64].

The duration of the first study was 9 weeks: two 4-week treatment periods with either vitamin B_6 or placebo and a 1-week washout. The 4-week periods were chosen based on previous reports of a decline in involuntary movements after four days to 1 week of treatment with vitamin B_6 [48, 55, 59–61]. Furthermore, this period provided an opportunity to exclude the influence of spontaneous fluctuations in the severity of TD. Since some publications report a return to normal concentrations of serum pyridoxine levels within 4 days after stopping vitamin B_6 supplementation, a 1-week washout period was included [65].

The doses of all psychotropic medications remained unchanged throughout the study. Vitamin B_6 dosage for the first week was 100 mg/day, 200 mg/day for the second, 300 mg/day for the third and 400 mg/day for the fourth week. During the first week vitamin B_6 or a placebo were administered in a single daily dose and from the second week of the study in twice daily divided doses.

All patients underwent a subsequent washout period of 1 week, after which they were crossed over to the alternative treatment for an additional 4 weeks. The medication treatment was carefully monitored in order to ensure compliance.

Tardive dyskinesia was assessed with the extrapyramidal symptom rating scale (ESRS) [65]. Assessments were performed at baseline and repeated every week.

Of the 27 patients who were screened for this study, 15 inpatients were enrolled (four males and eleven females). Their ages ranged from 28 to 71 years old (mean 50.0 years, SD = 14.2). The patients had suffered from TD for a period of 1–15 years (mean 5.2 years, SD = 4.2). All patients had been hospitalized for 1–3 years during which they had the standard balanced hospital diet, and no patients revealed clinically relevant signs of malnutrition. The participants' characteristics are presented in Table 6.2.

Table 6.2 Demographic data and clinic characteristic of patients

	Patients ($N = 15$)
Gender: (N)	
Female	11
Male	4
Age (years)	
Mean:	50.0 ± 14.22
Range:	20–71
Smoking	8
Nonsmoking	7
DSM-IV diagnosis:	
Schizoaffective Disorder	6
Paranoid Schizophrenia	9
Duration of illness (years)	
Mean:	18.6 ± 13.13
Range:	2–42
Duration of TD (years)	
Mean	5.2 ± 4.2
Range	1–15
Treatment: (mean, range, N)	
Haloperidol decanoate	462.5 ± 149.3; 250–600 mg/day; (4)
Fluphenazine decanoate	625 ± 176.8; 500–750 mg/day; (2)
Perphenazine	437.5 ± 228.7; 200–750 mg/day; (3)
Penfluridol	375 ± 106.1; 300–450 mg/day; (2)
Clozapine	550 mg/day; (1)
Risperidone	3 mg/day; (1)
Olanzapine	12.5 ± 5.0; 5–15 mg/day (4)
Lithium	1350 ± 636.4; 900–1800 mg/day (2)
Valproic acid	700 ± 424.2; 400–1000 mg/day (2)
Carbamazepine	900 mg/day; (1)
Trihexyphenidyl	4.18 ± 1.66; 2–6 mg/day; (7)
Biperiden	3.96 ± 1.87; 2–6 mg/day; (5)

The results of this study demonstrate that vitamin B_6 was well tolerated by all patients, and all were able to receive the maximal dose of 400 mg/day without any adverse effects.

The mean ESRS group scores on vitamin B_6 statistically improved ($p < 0.001$), beginning at the third week of treatment compared with scores during the placebo period. The improvement was demonstrated both in the parkinsonism and dyskinesia subscales (Tables 6.3 and 6.4).

With time, our clinical experience showed that the positive effect of vitamin B_6 on TD continued for a long period after stopping the higher dose of the medication, thus an additional aim of the study was the evaluation of the carryover effect of vitamin B_6.

In our next study, we decided to replicate the study and reexamine the efficacy and safety of higher doses of vitamin B_6 (1200 mg/day), vs. placebo on a larger sample of patients and for a longer period of time [64].

Fifty patients (28 men and 22 women), mean ± SD age was 47 ± 11 years (range 20–66 years) were enrolled into the study. Thirty four suffered from chronic schizophrenia and 16 from schizoaffective disorder. All patients had been hospitalized for 1–3 years. Most of them were smokers and suffered from TD less than 5 years. All patients were on a regular balanced hospital diet under supervision of a clinical dietician, and there were no clinically relevant symptoms of malnutrition. The patients' characteristics are presented in Table 6.5.

After baseline assessment, subjects were randomly assigned: each patient was given 2 tablets (300 mg each) of vitamin B_6 twice a day (1200 mg/day) or 2 tablets of placebo twice a day. The tablets were administered at 8 AM and 8 PM every day for 12 weeks (phase 1). After a 2-week washout period (following vitamin or placebo treatment) the patients were treated for the next 12 weeks with the other preparation (phase 2). Vitamin B_6 or placebo was given in addition to each patient's regular antipsychotic medication. A crossover design was used as an appropriate design for chronic patients in stable pathologic condition, in an attempt to reduce variance and increase effective sample size. Severity of movement disorders was assessed using the ESRS [67, 68]. Safety and tolerability of high dose vitamin B_6 were evaluated by assessing the incidence and severity of adverse events, for all patients who had received at least 1 dose of study medication during that phase, as well as withdrawals because of adverse events.

Vitamin B_6 was well tolerated by most of the patients, and they were able to receive the maximal dose of 1200 mg/day during the entire study. Only one patient demonstrated acne during the vitamin phase and another developed an allergic reaction (light itch) after 2-months of treatment. Of 50 randomized patients, 5 subjects did not comply with the treatment regimen after the first month of treatment since they did not want to add four more pills; therefore they were excluded from the statistical analysis. Of the 45 patients who completed the phase 1, 9 patients (5 on vitamin and 4 on placebo) dropped out before completing the first rating of the second phase of crossover (1 patient due to acne, 1 due to allergic reaction, both in spite of TD improvement, and 7 patients due to noncompliance). Thus, 36 patients completed both phases of the study.

Table 6.3 Parkinsonism subscale ratings of 15 patients before and during treatment with vitamin B_6 and placebo [65]

Period I						WO	Period II					Scheffe's Post Hoc test
Parkinsonism	Baseline *B(I)*	Visit 1 (100 mg) *T1*	Visit 2 (200 mg) *T2*	Visit 3 (300 mg) *T3*	Visit 4 (400 mg) *T4*		Baseline II *B(II)*	Visit 6 (100 mg) T6	Visit 7 (200 mg) T7	Visit 8 (300 mg) T8	Visit 9 (400 mg) T9	
Placebo followed Vitamin (Vp) (N = 8)	21.0 (10.5)	16.25 (8.7)	12.0 (8.3)	8.0 (6.25)	7.4 (4.0)		17.6 (6.8)	23.7 (9.9)	21.5 (4.0)	21.4 (8.2)	22.6 (10.2)	Vp(BI) ≠Vp(T3), Vp(T4) Vp(T4) ≠Vp(T6), Vp(T7), Vp(T8), Vp(T9)
Vitamin followed Placebo (Pv) (N = 7)	22.1 (10.7)	17.6 (9.2)	18.4 (8.1)	16.1 (5.5)	19.0 (7.5)		24.7 (8.0)	23.1 (8.4)	14.6 (6.1)	11.1 (4.7)	11.6 (5.9)	Pv(BII) ≠Pv(T8), Pv(T9)

Results are expressed as mean (SD). *WO* = washout period (1 week)
Three way ANOVA: fixed effects, repeated measure: Between: placebo vs vitamin B_6, Within: periods (period I vs period II), and visits (baseline, visit 1, visit 2, visit 3, visit 4)

Summary of all effect:
1. Treatment: $F(1,13) = 0.1$, $p < 0.75$ – NS
2. Period: $F(1,13) = 2.28$, $p < 0.154$ – NS
3. Visit: $F(4,52) = 10.43$, $P < 0.0000$
4. *Interaction:* treatment × period: $F(1,13) = 4.979$, $p < 0.043$
5. *Interaction:* treatment × visit: $F(4,52) = 1.05$, $p < 0.39$ – NS
6. *Interaction:* period × visit: $F(4,52) = 1.37$, $P < 0.257$ – NS
7. *Interaction:* treatment × period × visit: $F(4,52) = 7.54$, $p < 0.0000$

Table 6.4 Dyskinetic movements subscale ratings of 15 patients before and during treatment with vitamin B_6 and placebo [65]

Period I						WO	Period II					Scheffe's Post Hoc test
Dyskinetic movements	Baseline *B(I)*	Visit 1 (100 mg) *T1*	Visit 2 (200 mg) T2	Visit 3 (300 mg) *T3*	Visit 4 (400 mg) T4		Baseline II *B(II)*	Visit 6 (100 mg) T6	Visit 7 (200 mg) T7	Visit 8 (300 mg) T8	Visit 9 (400 mg) T9	
Placebo followed Vitamin (Vp) (N = 8)	7.1 (5.2)	5.0 (4.1)	3.6 (2.7)	2.1 (2.0)	2.3 (2.7)		7.7 (4.3)	8.4 (4.3)	8.1 (4.0)	8.0 (4.5)	8.3 (4.2)	Vp(BI) ≠Vp(T3), Vp(T4). Vp(T4) ≠ Vp(BII), Vp(T6),
Vitamin followed Placebo (Pv) (N=7)	7.6 (4.5)	7.4 (4.1)	8.5 (4.4)	8.0 (4.1)	8.0 (3.8)		8.1 (4.9)	7.1 (4.2)	6.0 (3.0)	3.9 (2.2)	4.0 (3.0)	Vp(T7), Vp(T8), Vp(T9). Pv(BII) ≠ Vp(T8), Vp(T9).

Results are expressed as mean (SD). *WO* = washout period (1 week)
Three way ANOVA: fixed effects, repeated measure: Between: placebo vs vitamin B6, Within: periods (period I vs period II), and visits (baseline, visit 1, visit 2, visit 3, visit 4)

Summary of all effect:

1. Treatment: $F(1,13) = 0.42$, $p < 0.53$ – NS
2. Period: $F(1,13) = 0.58$, $p < 0.46$ – NS
3. Visit: $F(4,52) = 6.2$, $P < 0.0004$
4. *Interaction:* treatment × period: $F(1,13) = 5.46$, $p < 0.031$
5. *Interaction:* treatment × visit: $F(4,52) = 0.26$, $p < 0.9$ – NS
6. *Interaction:* period × visit: $F(4,52) = 0.25$, $P < 0.9$ – NS
7. *Interaction:* treatment × period × visit: $F(4,52) = 8.0$, $p < 0.0000$

Table 6.5 Demographic data and clinic characteristic of patients [64]

		Randomization	
	Whole sample ($N = 50$)	Vitamin B_6 ($N = 28$)	Placebo ($N = 22$)
Gender: (N)			
Female	22	12	10
Male	28	16	12
Age (years)			
Mean:	46.8 ± 11.1	45.4 ± 12.3	48.5 ± 9.4
Range:	20–66	20–62	29–66
Smokers	46	26	20
Nonsmokers	4	2	2
DSM-IV diagnosis:			
Schizophrenia	34	18	16
Schizoaffective disorder	16	10	6
Duration of illness (years)			
Mean:	19.0 ± 10.9	18.6 ± 10.0	19.5 ± 9.2
Range:	2–41	2–41	4–34
Duration of TD (years)			
< 3	28	16 (57%)	12 (54%)
3–5	10	5 (18%)	5 (23%)
>5	12	7 (25%)	5 (23%)
Treatment: (N)			
Typical antipsychotics	31	16 (57%)	15 (68%)
Atypical antipsychotics	19	10 (36%)	9 (41%)
Mood stabilizers	18	11 (39%)	7 (32%)
Anticholinergic agents	25	13 (46%)	12 (54%)

Results are expressed as mean and SD
There were not significant differences on randomization

The results of our study demonstrated that vitamin B_6 had a highly significant therapeutic effect in the parkinsonism, dyskinetic and CGI subscales. The parkinsonism scores diminished from baseline (28.3) to endpoint (9.8) during vitamin B_6 treatment by 18.5 points and only by 1.4 points (from 26.8 to 25.4) during placebo treatment, $p = 0.00001$. Significant improvement on the parkinsonism subscale appeared on the 12th week of treatment with vitamin B_6, $p < 0.01$. Symptoms of tardive dyskinesia diminished by 5.2 points from baseline (9.9) to the endpoint (4.7) in patients treated with vitamin B_6, in contrast to patients who received placebo whose scores increased by 0.8 points (from 6.6 to 7.4 points), $p = 0.00009$). The CGI rates diminished by 2.4 points (from 4.3 to 1.9) and revealed almost no change on placebo – 4.1 at baseline and 3.9 at endpoint, $p < 0.0001$. Improvement was significant from the 8th week, $p < 0.01$ (Table 6.6).

Table 6.6 Efficacy of vitamin B_6 vs. placebo in schizophrenic patients with tardive dyskinesia in period I (ESRS subscales analysis, mean ± SEM, $n = 45$) [64]

			Time						
ESRS subscales	Treatment	Baseline*	Week 2	Week 4	Week 8	Week 12	Treatment effect (df = 1,43)	Time (df = 4,172)	Time-treatment interaction (df = 4,172)
Parkinsonism	Vitamin $N = 23$	28.3 ± 2.1	18.0 ± 2.5	14.1 ± 2.4	11.6 ± 2.1	9.8 ± 2.0**	$F = 10.7$; $p < .002$	$F = 24.6$; $p < .00001$	$F = 13.1$; $p < 0.00001$
	Placebo $N = 22$	26.8 ± 2.2	25.5 ± 2.6	24.4 ± 2.4	23.9 ± 2.2	25.4 ± 2.1			
CGI of Parkinsonism	Vitamin $N = 23$	5.3 ± 0.4	4.1 ± 0.4**	3.3 ± 0.4***	2.7 ± 0.4***	2.4 ± 0.4***	$F = 12.0$; $p < 0.001$	$F = 21.9$; $p < 0.0001$	$F = 7.8$; $p < 0.00001$
	Placebo $N = 22$	5.5 ± 0.3	5.3 ± 0.3	4.9 ± 0.4	4.7 ± 0.4	5.0 ± 0.3			
Tardive Dyskinesia	Vitamin $N = 23$	9.9 ± 1.5	7.6 ± 1.3	6.4 ± 1.1	5.3 ± 1.2	4.7 ± 0.9	$F = 0.09$; $p = 0.760$	$F = 3.6$; $p < 0.0002$	$F = 6.3$; $p < 0.00009$
	Placebo $N = 22$	6.6 ± 1.5	7.4 ± 1.2	7.7 ± 1.3	7.2 ± 1.4	7.4 ± 1.3			
CGI of TD	Vitamin $N = 23$	4.4 ± 0.5	3.7 ± 0.5	3.1 ± 0.4	2.4 ± 0.5	2.1 ± 0.4**	$F = 0.5$; $p = 0.48$	$F = 10.0$; $p < 0.0001$	$F = 6.9$; $p < 0.00003$
	Placebo $N = 22$	3.5 ± 0.5	3.9 ± 0.5	3.8 ± 0.5	3.4 ± 0.5	3.4 ± 0.5			
Clinical global impression	Vitamin $N = 23$	4.3 ± 0.2	3.5 ± 0.2	3.0 ± 0.2	2.3 ± 0.2**	1.9 ± 0.2***	$F = 13.3$; $p < 0.0001$	$F = 29.5$; $p < 0.0001$	$F = 20.1$; $p < 0.0001$
	Placebo $N = 22$	4.1 ± 0.2	4.0 ± 0.2	4.0 ± 0.2	3.9 ± 0.3	3.9 ± 0.2			

*No difference between groups baseline $p > 0.05$
**LSD Post Hoc Test $p < 0.025$
***LSD Post Hoc Test $p < 0.01$
ESRS – Extrapyramidal Symptom Rating Scale
SEM – Standard Error
CGI – Clinical Global Impression
TD – Tardive dyskinesia

In contrast to phase 1, in which the baseline scores of both groups were identical, in phase 2 the starting scores were different due to the influence of the carryover effect of previous vitamin therapy. Changes in clinical impression and ESRS scores showed that vitamin B_6 was significantly more effective than placebo: symptoms of tardive parkinsonism decreased by 14.9 ± 1.5 units from baseline to endpoint, and -4.9 ± 1.8 units on placebo, $p < 0.00001$; dyskinetic symptoms were diminished from baseline to endpoint on 4.2 ± 0.8 units during vitamin treatment, and -2.9 ± 0.9 during placebo, $p < 0.0003$; CGI rates on 2.0 ± 0.2 during vitamin treatment in contrast to -0.6 ± 0.2 on placebo, $p < 0.00001$. A significant difference on the parkinsonism subscale demonstrated improvement from the fourth week of vitamin B_6 treatment, $p < 0.004$; on the dyskinetic subscale the significant improvement appeared from the 8th week of treatment with vitamin B_6, $p < 0.01$). The CGI subscale showed a significant positive effect from the 4th week of vitamin B_6 treatment, $p < 0.004$ (Table 6.7).

Continuous beneficial effect of vitamin B_6 was observed in all ESRS subscales but the most prominent impressive significance was demonstrated in the CGI subscale (Fig. 6.1). After 2 weeks of washout period, the patients with placebo substitution in the second phase, showed no significant difference in CGI ratings until the fourth week. Immediately following this period of time the CGI score returned to the pre-vitamin treatment state and at the 12th week they reverted to approximate baseline ESRS scores (Fig. 6.4).

The results of this double-blind placebo-controlled study suggest that a high dose (1200 mg/day) of vitamin B_6 is an effective and safe treatment for TD. This dosage of vitamin B_6 acts for a longer period (approximately 8 weeks after cessation) in comparison to lower doses (400 mg/day), which were also found to be effective but not for more than 1 week after end of treatment [68].

Our extended experience (more than 8 years) with the use of high doses of vitamin B_6 led us to conclude that the dose of 1200 mg/day is safe. None of subjects demonstrated any neurotoxic side effect during all these years.

Vitamin E (Alpha-Tocopherol)

Vitamin E is a lipid-soluble antioxidant located on cell membranes near enzymes that produce free radicals [69–73]. During the last three decades about 40 trials were performed in order to examine the efficacy of vitamin E on TD. The results of these studies were contradictory. Lohr and colleagues performed two double-blind trials [74, 75]. In one [74] the authors treated 15 patients with persistent TD with 1200 I.U. of vitamin E daily and found an average 43% decrease in the Abnormal Involuntary Movement Scale (AIMS) scores. The seven patients who showed a > 50% response had a shorter duration of TD than did the eight patients with <50% improvement. In another study [75], 35 patients completed a double-blind placebo-controlled parallel-group study of vitamin E. The overall reduction in AIMS in the active group was 24%, with 5 (29%) of 17 patients demonstrating greater than 33%

Table 6.7 Efficacy of vitamin B_6 vs. placebo in schizophrenic patients with tardive dyskinesia who completed the whole crossover study (ESRS subscales analysis, mean ± SEM, $n = 36$) [64]

			Improvement (Δ from baseline)						
ESRS subscales	Treatment	Baseline*	Week 2	Week 4	Week 8	Week 12	Treatment effect (df = 1,34)	Treatment × time (df = 3,102)	Treatment × time × order interaction (df=3,102)**
Parkinsonism	Vitamin	24.1 ± 1.8	5.6 ± 0.9	10.3 ± 1.2***	12.6 ± 1.3***	14.9 ± 1.5***	$F = 45.3$; $p < 0.00001$	$F = 25.0$; $p < 0.00001$	$F = 2.3$; $p < 0.09$
	Placebo	19.8 ± 2.0	–0.7 ± 1.1	–1.8 ± 1.5	–3.3 ± 1.8	–4.9 ± 1.8			
CGI of Parkinsonism	Vitamin	5.1 ± 0.2	1.1 ± 0.2**	1.9 ± 0.3***	2.4 ± 0.3***	2.6 ± 0.3***	$F = 31.0$; $p < 0.00001$	$F = 13.9$; $p < 0.00001$	$F = 2.5$; $p = 0.07$
	Placebo	4.1 ± 0.4	–0.2 ± 0.2	–0.3 ± 0.3	–0.4 ± 0.4	–0.5 ± 0.4			
Tardive Dyskinesia	Vitamin	8.7 ± 1.1	1.4 ± 0.5	2.7 ± 0.7	3.8 ± 0.9**	4.2 ± 0.8**	$F = 17.9$; $p < 0.0001$	$F = 8.7$; $p < 0.0003$	$F = 2.2$; $p < 0.09$
	Placebo	5.9 ± 1.0	–1.3 ± 0.6	–2.1 ± 0.9	–2.9 ± 1.0	–2.9 ± 0.9			
CGI of TD	Vitamin	3.8 ± 0.4	0.5 ± 0.2	1.2 ± 0.3***	1.6 ± 0.3***	1.9 ± 0.3***	$F = 25.6$; $p < 0.00001$	$F = 9.4$; $p < 0.00001$	$F = 6.8$; $p < 0.001$
	Placebo	3.0 ± 0.3	–0.4 ± 0.2	–0.7 ± 0.2	–0.6 ± 0.3	–0.8 ± 0.3			
Clinical global impression	Vitamin	4.0 ± 0.1	0.7 ± 0.1	1.2 ± 0.2**	1.7 ± 0.2***	2.0 ± 0.2***	$F = 60.6$; $p < 0.0001$	$F = 26.5$; $p < 0.0001$	$F = 6.2$; $p < 0.0001$
	Placebo	3.2 ± 0.2	–0.8 ± 0.1	–0.3 ± 0.2	–0.5 ± 0.2	–0.6 ± 0.2			

*No difference between groups baseline $p > 0.05$
**LSD Post Hoc Test $p < 0.01$
***LSD Post Hoc Test $p < 0.005$
ESRS – Extrapyramidal Symptom Rating Scale
SEM – Standard Error
CGI – Clinical Global Impression
TD – Tardive dyskinesia

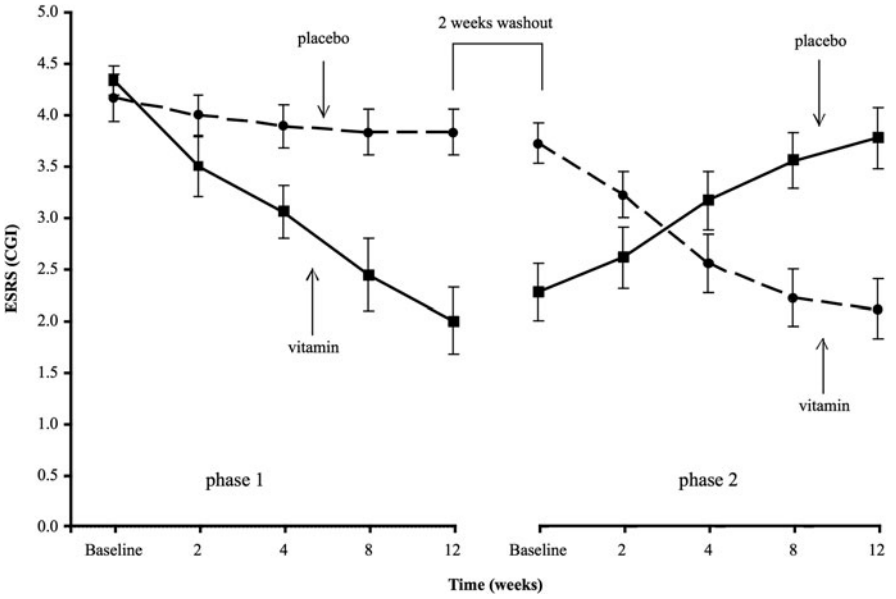

Fig. 6.4 CGI subscale during the crossover design treatment. Vitamin B_6 vs placebo (Mean ± SEM; $N = 36$) [64]. Treatment–time interaction: $F = 26.5$, df = 3,102, $p < 0.00001$; LSD post Hoc test for 4th week, $p < 0.004$

reduction in score. There was a greater reduction in mean AIMS score (35%) with vitamin E in the subgroup of patients with TD for 5 years or less compared with the reduction (11%) in patients with TD for more than 5 years. No change was observed in parkinsonism. The authors concluded that vitamin E appears to be effective in reducing the severity of TD, especially in patients who have had TD for 5 years or less.

In a 36-week double-blind study Adler and colleagues compared the influence of vitamin E (1600 IU per day) and placebo on TD's symptoms in 40 patients using the Abnormal Involuntary Movements Scale (AIMS). The study's finding that vitamin E is effective in treating TD agrees with results from prior studies and provides evidence that the effect may extend to treatment of up to 36 weeks [76].

Aside from this 36 week trial, most of the above mentioned studies were small and lasted only 4–12 weeks.

Contrary to the positive findings regarding the efficacy of vitamin E on TD, there are a number double-blind trials with negative results [77–79], including ours [80]. For example, in another, much larger, long-term, multi-site study, conducted by Adler and many of the same investigators, the superiority of vitamin E to placebo was not demonstrated [77]. Egan with coworkers performed a 6 week, a double-blind, placebo-controlled crossover study which included 21 patients with TD. All subjects received up to 1600 IU/day of vitamin E. The authors did not find significant differences between AIMS scores after receiving the vitamin.

It should be noted that in different reviews of double-blind studies concerning the efficacy of vitamin E in the treatment of TD, authors also reached opposing conclusions. Thus, Boomershine et al. [69] analyzed 18 completed trials and found that 12 of them produced positive results with vitamin E in the treatment of TD. Based on this analysis, the authors concluded that patients who had TD for less than 5 years appear to respond better than patients with long-standing TD. A meta analysis of published studies showed that a significant subgroup (28.3%) of patients with TD who were treated with vitamin E showed modest improvement [81]. The impression gained from these studies is that, while vitamin E is safe and well-tolerated, it confers only modest benefits.

On the other hand, Soares and McGrath [82] analyzed all controlled trials dealing with people with neuroleptic-induced TD suffering from schizophrenia or other chronic mental illness who had been randomly allocated to either vitamin E or to a placebo. They concluded that vitamin E protects against deterioration of TD, but there is no evidence that vitamin E improves symptoms of TD. Trials of longer duration may yield better results. According to their opinion, additional studies will need to address the mechanism responsible for the therapeutic effects of vitamin E on TD.

Melatonin in Treatment of TD

Melatonin (N-acetyl-5 methoxytryptamine) is an endogenous hormone produced mainly in the pineal gland, but some is also synthesized in the retina, bone marrow and lymphocytes. It is not only a natural mammalian hormone, it is widely found in nature, including foods such as oats [83, 84]. Melatonin has a variety of seemingly unrelated functions in organisms. It is involved in a number of 24 h rhythms and is believed to be an important component of the circadian system and attenuates dopaminergic activity in the striatum and dopamine release from the hypothalamus. Melatonin is now known to be a multifaceted free radical scavenger and antioxidant. It has been shown to markedly protect both membrane lipids and nuclear DNA from oxidative damage. In every experimental model in which melatonin has been tested, it has been found to resist macromolecular damage and the associated dysfunction associated with free radicals [85, 86].

Melatonin has been shown to be highly effective in reducing oxidative damage in the central nervous system; this efficacy derives from its ability to directly scavenge a number of free radicals and to function as an indirect antioxidant. One additional advantage melatonin has in reducing oxidative damage in the central nervous system is the ease with which it crosses the blood-brain barrier. This combination of these actions makes melatonin a highly effective pharmacological agent against free radical damage [85–87]. It has been suggested that melatonin may have a beneficial effect for both the treatment and prevention of TD.

To date, there have been only a few clinical trials with inconclusive results. Shamir and colleagues [87, 88] attempted to assess the treatment effectiveness of

melatonin for TD. In the first study [87] a group of 19 elderly patients aged 65 years or older suffering from chronic schizophrenia were randomly assigned in a double-blind, placebo-controlled, crossover trial to receive slow-release melatonin, 2 mg/day, or placebo for 4 weeks. Between treatments the patients underwent a 2-week washout period and were then switched to the other treatment arm for an additional 4 weeks. The AIMS was administered at baseline, 4 weeks, 6 weeks, and 10 weeks. Regular administration of antipsychotic and other medications was kept unchanged throughout the study. Following completion of the study by all participants the mean AIMS scores did not change significantly from baseline in either treatment arm. There were no side effects or adverse events. The authors concluded that supraphysiologic doses of melatonin do not positively affect TD.

A year later the same authors published the results of a second attempt to investigate the effects of melatonin treatment for TD [88]. Using a double-blind, placebo-controlled, crossover study, they evaluated the efficacy of 10 mg/d of melatonin for 6 weeks in 22 patients with both schizophrenia and significant tardive dyskinesia. The primary outcome measure was the change from baseline in the AIMS score. Indeed, the decrease in AIMS score was 2.45 ± 1.92 for the melatonin and 0.77 ± 1.11 for the placebo treatment groups ($P < 0.001$). Treatment was safe and well tolerated by all patients.

The Natural Medicines Comprehensive Database states that taking melatonin orally 10 mg daily seems to decrease symptoms by 24–30% in some patients with TD after 6 weeks of treatment [89].

In 2003, Nelson and colleagues reviewed the available literature (1966–September 2002) regarding the use of melatonin in the treatment of TD. The authors concluded that the efficacy of melatonin appears to be dose dependent, with lower doses showing little to no improvement in this disorder. According to their opinion, more studies are needed to determine if higher doses of melatonin will provide greater efficacy and also to determine the recommended length of therapy. To date there is a lack of data evaluating the use of melatonin in tardive dyskinesia [90].

Ginkgo Biloba in Treatment of TD

Ginkgo biloba is one of the oldest living tree species. The plant is commonly known as the maiden hair tree. For centuries, extracts from the leaves of the ginkgo biloba tree have been used as Chinese herbal medicine to treat a variety of medical conditions. Today, ginkgo leaf extract is one of the top selling herbs in the United States (retail sales of US $150 million in 1998) [91] and its leaves are among the most extensively studied botanicals in use today. Ginkgo leaves contain two types of chemicals (flavonoids and terpenoids) believed to have potent antioxidant properties [92, 93]. Ginkgo is believed to have nootropic properties, and is mainly used as memory and concentration enhancer, and anti-vertigo agent [94]. It is used for the treatment of numerous conditions, many of which are under scientific investigation. It has been widely used to treat cerebrovascular and peripheral vascular

insufficiency (intermittent claudication), as well as the cognitive and functional symptoms associated with mild to moderate dementia [95].

Regarding the efficacy of ginkgo biloba there are opposite results. Some studies demonstrate that it may be effective in the management of Alzheimer's or vascular dementia and improves blood circulation and oxygenation of brain cells [95–98]. However, the largest and longest independent clinical trial to assess ginkgo biloba's ability to prevent memory loss has found that the supplement does not prevent or delay dementia or Alzheimer's disease [99–101].

EGb-761 is a standardized extract of ginkgo biloba leaves that has antioxidant properties as a free radical scavenger [95]. The antioxidant properties and free radical-scavenging actions of EGb-761 have been proposed to underlie its beneficial effects [102].

Zhang and coworkers examined the efficacy of EGb-761 as add-on treatment to haloperidol in patients with schizophrenia and found that this combination led to a reduction of extrapyramidal side effects [103]. At the next step the same authors decided to investigate more specifically EGb-761's influence on TD symptoms [104]. In this study 157 patients were enrolled and randomly assigned to 12 weeks of treatment with either EGb-761, 240 mg/d ($n = 78$), or placebo ($n = 79$) in a double-blind mode. Severity of TD was assessed using the Abnormal Involuntary Movement Scale (AIMS). The results of this trial demonstrate that EGb-761 treatment significantly decreased the total AIMS score in patients with TD compared to those who received placebo (2.16 ± 1.75 versus -0.11 ± 1.74; $p < 0.0001$). In the treatment group 52% of the patients showed significant improvement, compared to 5.3% in the placebo group. The authors conclude that EGb-761 appears to be an effective treatment for reducing the symptoms of TD in schizophrenia patients, and improvement may be mediated through the well-known antioxidant activity of this extract.

Omega-3 in Treatment of TD

Omega-3 (omega-3) is an essential fatty acid (EFA) found in large amounts in fish oil. It contains eicosapentaenoic acid (EPA) and docosahexaenoic acid which are essential to human health but cannot be manufactured by the body. Omega-3 fatty acids are long-chain polyunsaturated fatty acids of plant and marine-origin. Omega-3 fatty acids are built-in into the cell membrane affecting the function of neurotransmitter receptors. A relation appears to exist between omega-3 fatty acids and central nervous system (CNS) neurotransmitters and especially between them and the serotonin system via protein kinase inhibition [105, 106]. Omega-3 fatty acids are believed to stimulate the neurotrophic factor, to increase synaptic plasticity, improve neurotransmission, and to have antidepressant and neuroprotective properties [107]. A neuroprotective effect of omega-3 fatty acids helps the brain to repair damage by promoting neuronal growth. Preliminary animal studies provide strong support for a therapeutic effect of omega-3 EFA supplemented to the classical

neuroleptic regimen in the treatment of schizophrenic symptoms and tardive dyskinesia [108].

On this basis, it has been hypothesized that EPA may have a role in the treatment of TD. In Some clinical trials revealed a structural beneficial impact of omega-3 supplementation in some neurological diseases, including TD [109–111]. However, comparison of EPA and placebo in a double-blinded, randomized, parallel group study performed by Emsley and coworkers [112] in 77 schizophrenia and schizoaffective patients suffering from TD, failed to demonstrate an antidyskinetic effect for ethyl-EPA 2 g/day on the primary efficacy measure (ESRS). The researchers explained their negative results by an insufficient dose of EPA, the underpowered study, chronicity of TD in the majority of cases and differences in dietary fatty acid intake. Further, the authors do not rule out that EPA indeed lacks an antidyskinetic action.

In a recent review by Vaddadi and colleagues [113], the reviewers concluded that supplementation with EFAs (omega-3 and omega-6 and ethyl-EPA) have been investigated to alleviate TD in open and double-blind clinical trials and in some animal models of TD. However, small numbers of patients and short duration of clinical studies make it difficult to draw any definitive conclusions. They assumed that large multi-centre studies with sound methodology of both EFAs and antioxidants are needed.

Conclusions

In this chapter we review the current knowledge regarding some antioxidants in the treatment of TD. Based on the literature and on our clinical and research experience, our impression is that these substances have potential in the management of this iatrogenic movement disorder. There is no consensus regarding many aspects of TD such as incidence or prevalence, its cause and neurophysiology. To date, no pharmacologic treatment has been proven to be universally or even typically effective in the treatment of TD in clinical practice. The search for effective and definitive treatment for TD is an important therapeutic challenge and is relevant to all clinicians that treat patients with this condition. A solution is warranted.

The adage “to prevent maladies is much easier, than to treat them” merits agreement. More than 20 years ago, Hawkins reported success in the prevention of TD in 61.508 patients using vitamins B_3, B_6, C, and E [114, 115]. His results were based on reports from 80 psychiatrists, who routinely used high-dose vitamins along with drugs to treat people with schizophrenia. According to his data during a 20 year longitudinal study using high dose of vitamins in addition to typical neuroleptics (vitamin C – 3 g/day, vitamin B_3 – 3 g/day, vitamin B_6 – 400 mg/day, and vitamin E – 400 I.U.). The results are far fewer than might be expected: it showed that only 34 patients (0.05%) developed TD in comparison to an average rate of 30%.

This iatrogenic condition is at the interface between psychiatry and neurology. In general, psychiatric patients develop TD, while TD, being a movement disorder, is in

the competence of neurology. Another challenge is that TD is a heterogeneous entity with respect to its clinical features, topography, and pathophysiology. Moreover, most cases of TD also involve an underlying psychiatric disorder, which has a strong influence on the development, course, and treatment of TD.

We are aware that this is only the beginning on the long road towards discovery for a definitive treatment for this disturbance, but every trek begins with the first step. Clearly, further investigations regarding the efficacy of antioxidants in treating psychotropic-induced movement disorders and the potential effect in treating schizophrenia, are indicated.

Thus it is important to consider the validity of using vitamins and antioxidant agents in the treatment and prevention of this TD. It is possible that combined use of different antioxidants will be successful in the management of this disorder.

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Chapter 7
Electrophysiological Imaging Evaluation of Schizophrenia and Treatment Response

Tomiki Sumiyoshi, Yuko Higuchi, Toru Ito, and Yasuhiro Kawasaki

Abstract Neuroimaging data provide various insights into altered functions and structures in the brain of subjects with schizophrenia. While some blood flow measures, e.g. functional magnetic resonance imaging and positron emission tomography, are characterized by high spatial resolutions, their time resolutions are in the range of second order. In contrast, electromagnetic recordings, e.g. electroencephalography (EEG) and magnetoencephalography, directly detect neural activity that occurs in the range of milli-second order. In spite of its feasibility, analysis with traditional EEG methods has been associated with the limited ability to localize aberrant signals. However, the recent development of imaging technique, such as low resolution electromagnetic tomography (LORETA) and its modified versions (e.g. sLORETA), improves the spatial resolution of EEG at rest and event-related potentials (ERPs), such as P300 and mismatch negativity by providing three-dimensional distribution pattern of these electrophysiological activities. In this chapter, the authors present recent findings from electrical neuroimaging studies of schizophrenia in relation to the neural basis of psychotic symptoms and cognitive deficits of the illness, as well as treatment response. These research areas are likely to facilitate the development of practical and reliable biomarkers to predict symptom severity, improve long-term outcome, and pave a new avenue to early intervention of schizophrenia.

Keywords EEG · Event-related potentials · P300 · MMN · Neuro imaging · LORETA · Cognition · Schizophrenia

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Abbreviations

AAPDs	Atypical antipsychotic drugs
EEG	Electroencephalography
LORETA	Low resolution electromagnetic tomography
MMN	Mismatch negativity

Introduction

There is considerable evidence for associations between social functioning/community outcome and cognitive function, as evaluated by neuropsychological tests, such as the MATRICS Consensus Cognitive Battery in patients with schizophrenia [1]. Therefore, neural substrates underlying impaired cognitive performance need to be elucidated, particularly for the development of novel therapeutic methods for the illness.

While brain imaging methods based on blood flow, e.g. functional magnetic resonance imaging and positron emission tomography, are characterized by high spatial resolutions, their time resolutions are limited compared to neurophysiological paradigms, e.g. electroencephalography (EEG) and magnetoencephalography. Specifically, electrophysiological biomarkers, such as EEG and event-related potentials (ERPs), have been suggested to provide objective indices of cognitive dysfunction in schizophrenia, and be more sensitive to drug-induced changes compared with other functional imaging modalities [2].

Recent development of imaging technique, such as low resolution electromagnetic tomography (LORETA) [3] and its modified versions (e.g. sLORETA) [4], has improved the spatial resolution of ERPs, e.g. P300 and mismatch negativity (MMN), by providing three-dimensional distribution pattern of these electrophysiological activities. This chapter provides recent findings from electrical neuroimaging studies on neural basis for psychopathology of schizophrenia as demonstrated by current source imaging of EEG and ERPs in discrete brain areas, and response to psychotropic drugs in relation to cognition and functional outcome.

LORETA Imaging of EEG in Schizophrenia

Scalp distributions of EEG power of various frequency bands are generally ambiguous [5], and depend on the reference sites used. Therefore, numerical analyses, such as dipole source modeling, are required to obtain precise locations of EEG generators.

LORETA has been developed to provide three-dimensional tomography of brain electrical activity, which only requires simple constraints (“smoothness of the solution”), and predetermined knowledge about the putative number of discernible source regions is not necessary (Fig. 7.1). With this method, brain electrical data

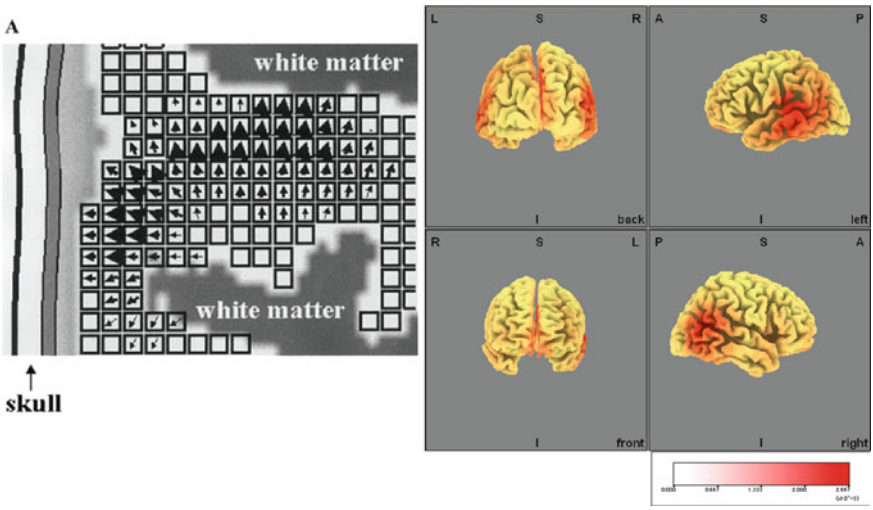

Fig. 7.1 Concept of low resolution electromagnetic tomography (LORETA) developed by Pascual-Marqui [3]. Three-dimensional imaging of LORETA values [mA/mm^2] is derived from 2394 voxels of the whole brain [8]

with high time resolution are transformed into functional imaging of brain activities, since brain electrical activity can be analyzed separately for the different EEG frequency ranges. LORETA has also been widely used for statistical comparisons of intracranial current density distributions between control subjects and patients with neuropsychiatric disorders [6, 7].

Previous investigations [3, 8] suggest that enhanced delta band activity in the prefrontal cortex is associated with the pathophysiology of schizophrenia. Specifically, negative symptoms have been associated with structural impairment in the prefrontal cortex, and have been hypothesized to arise from decreased dopaminergic activity in this brain region [9]. These observations indicate a role for prefrontal cortex in the generation of negative symptoms. With these backgrounds, we sought to determine if some components of EEG, such as delta band activity, would be increased in brain areas relevant to the pathophysiology of schizophrenia, e.g. prefrontal cortex.

As shown in Fig. 7.2 comparisons of current source density, as represented by LORETA values, between patients with schizophrenia and healthy control subjects revealed a significant increase in delta band activity for patients, with a maximum difference found at the left inferior temporal gyrus. A significant increase in delta band activities was also found for the right middle frontal gyrus, right inferior frontal gyrus, right superior frontal gyrus, and right parahippocampal gyrus. These data suggest LORETA analysis of three-dimensional distribution of EEG current density provides a measure of aberrant electrophysiological activity specific to the brain regions responsible for the manifestation of negative symptoms.

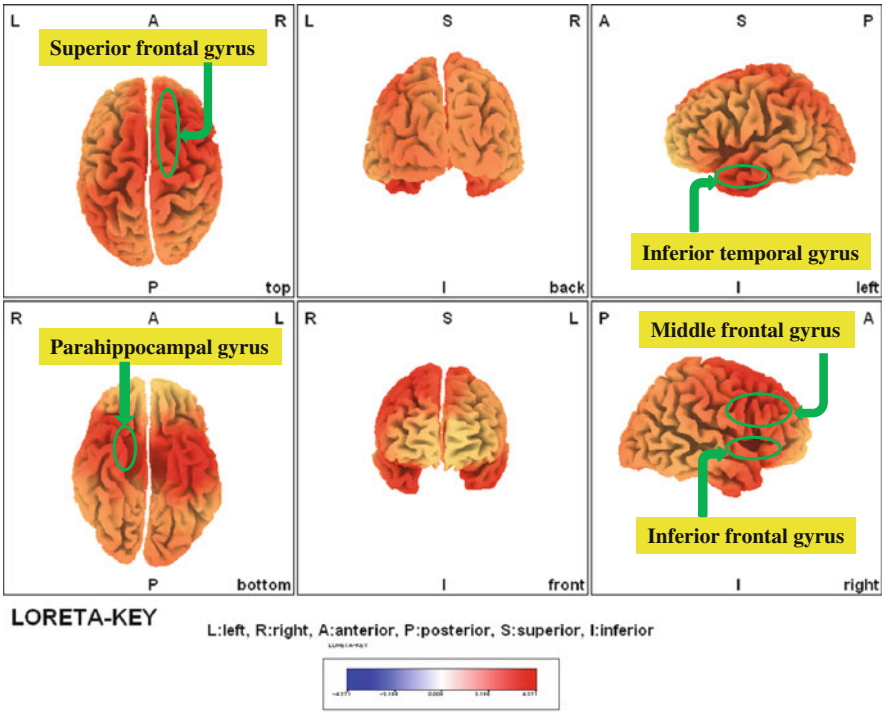

Fig. 7.2 LORETA current source density of *delta* band activity is increased in schizophrenia ($P < 0.001$, Bonferoni correction)

P300 Current Source Imaging and Psychopathology

Reduced amplitude of the P300 component during the auditory oddball task is one of the most consistent findings in patients with schizophrenia [10–12] (Fig. 7.3). However, little information is available about exact relationship between the clinical symptomatology of schizophrenia and the neurophysiological disturbances underlying the P300 abnormality. It is reasonable to assume that anatomically distinct neural substrates responsible for positive or negative symptoms independently contribute to the generation of the P300 component, because this ERP measure is thought to be a composite representation of neural activity in anatomically distinct generators [13–16].

To test this hypothesis, LORETA was used to compute the voxel-wise distribution of brain electrophysiological activity of the P300 component in order to identify brain regions in which the P300 current density is correlated with severity of psychotic symptoms of schizophrenia. Then, we applied the statistical parametric mapping (SPM) methods [17] to LORETA current density images of the P300 component [18, 19].

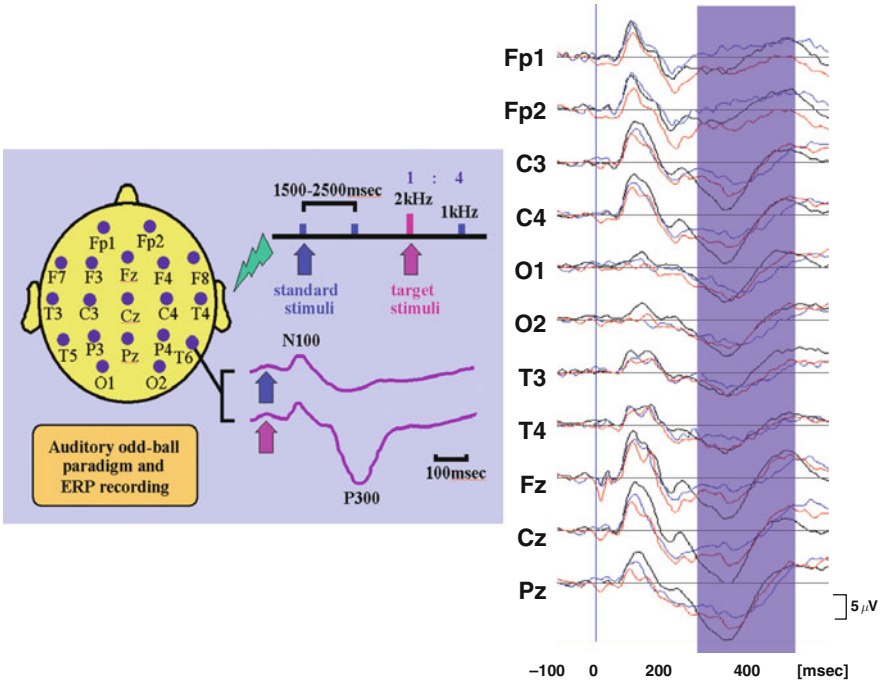

Fig. 7.3 Impaired P300, an event-related potential (ERP), as an endophenotypic marker of schizophrenia. In the right figure, black lines represent data for normal controls, while blue and red lines indicate data for patients before and after treatment with olanzapine, respectively

Results of the SPM one-sample t-test showed that P300 sources are localized in the bilateral medial frontal and medial parietal cortex, bilateral superior temporal gyrus (STG), right temporo-parietal junction, and left lateral prefrontal cortex. With regard to the relationship between the P300 current density and the BPRS Total score, voxel-based whole brain analysis without any hypothesis identified peak voxels of significant negative correlation located at the left STG and right medial frontal region. As shown in Fig. 7.4 (*left*), statistically significant voxels formed clusters within these brain regions. Mean current density values of the cluster in the STG elicited significant relationships with the Positive subscale score Fig. 7.4 (*right*). On the other hand, current density values of the cluster in the medial frontal region revealed a significant relationship with the Negative subscale score.

These findings indicate pathological neural activities of anatomically distinct generators contribute to the generation of the abnormal P300 component [20]. Our data were consistent with the proposal that negative symptoms are associated with neural deficits in the frontal lobe, while those in the temporal lobe are responsible for positive symptoms [21–23]. Taken together, the present results support the concept that the abnormal functional connectivity of fronto-temporal neural network plays a crucial role in the pathophysiology of schizophrenia [24–27].

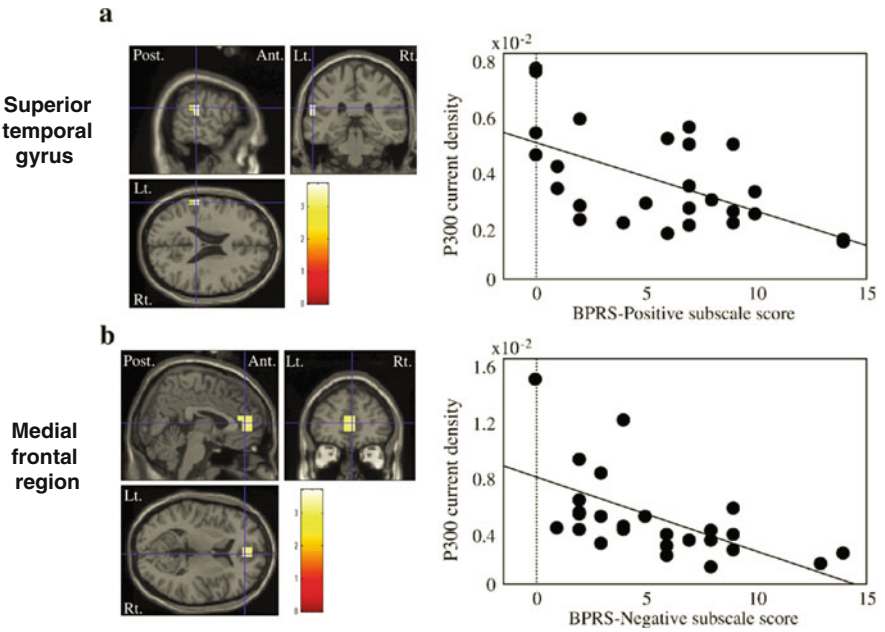

Fig. 7.4 Severity of psychotic symptoms is correlated with P300 current source density in discrete brain regions: A LORETA study [20]

ERPs Activity in Discrete Brain Regions and Effect of Neuroleptic Treatment

P300 amplitudes have been reported to be diminished in patients with schizophrenia, which differs in its effect size topography across the midline and temporal electrode sites [11, 28]. Specifically, Kawasaki et al. [29] found negative correlations between auditory P300 amplitudes and severity of psychotic symptoms of schizophrenia. Renoult et al. [30] report a positive correlation between differences in P300 amplitudes at temporal sites (T4-T3) and severity of positive symptoms and worse global functioning, consistent with the association between low P300 amplitudes and verbal memory deficits in schizophrenia [31, 32]. We reported the first observation that P300 current source density, as evaluated by LORETA, is decreased in several brain regions, especially the STG, precentral gyrus, middle frontal gyrus, and presumes (all in the left side) in patients with schizophrenia as compared with normal controls (Fig. 7.5) [33]. Our findings have been confirmed by an independent group of investigators [34].

Cognitive function, such as verbal memory, attention, and executive function, is a major determinant of outcome in patients with schizophrenia [35, 36]. The second generation antipsychotics, or so-called "atypical antipsychotic drugs (AAPDs)", have been found to partially improve cognitive disturbances of schizophrenia [37]. There is accumulated evidence for the ability of AAPDs, e.g. clozapine, olanzapine, risperidone, quetiapine, melperone, and ziprasidone and perospirone to ameliorate

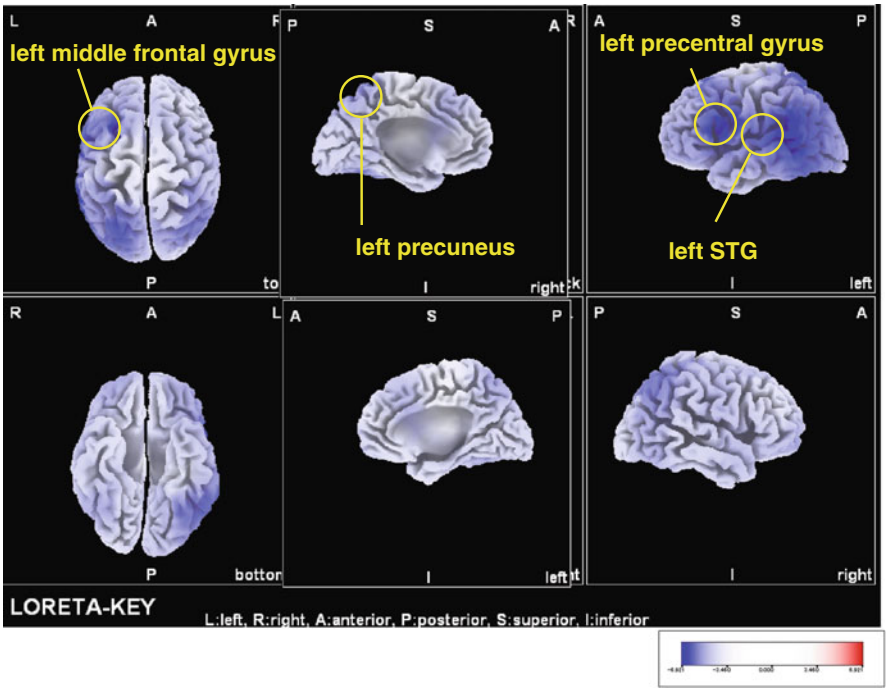

Fig. 7.5 Statistical non-parametric mapping on LORETA images of P300 current density. LORETA values in the marked areas in the left hemisphere were lower for schizophrenia patients compared to control subjects ($P < 0.001$) [33]

cognitive impairments in patients with schizophrenia (reviewed by Sumiyoshi et al. [38]), although their effects have been under scrutiny [39–41]. So far, there is limited information about the neurophysiological mechanisms underlying the ability of neuroleptic treatment to modulate cognitive performance in subjects with schizophrenia.

Umbricht et al. [42] found that treatment with clozapine but not haloperidol increased P300 amplitudes in patients with schizophrenia. Subsequently, Niznikiewicz et al. [43] observed an increase in P300 amplitudes in left temporal electrodes during treatment with clozapine, indicating a region-specific response to pharmacological treatment. We conducted clinical trials [33, 44] to determine if decreased P300 current source density in brain regions responsible for the generation of psychopathology, such as the left STG and prefrontal cortex, is recovered by long-term treatment with olanzapine, and if this change in P300 activity is correlated with improvement of cognitive performance and functional outcome in patients with schizophrenia.

As shown in Fig. 7.6 LORETA images of P300 from patients at baseline elicit lower P300 current density in the left hemisphere compared with normal controls. However, after 6-months treatment with olanzapine, P300 current density in the STG was increased, and the left-dominant laterality pattern of P300 current source

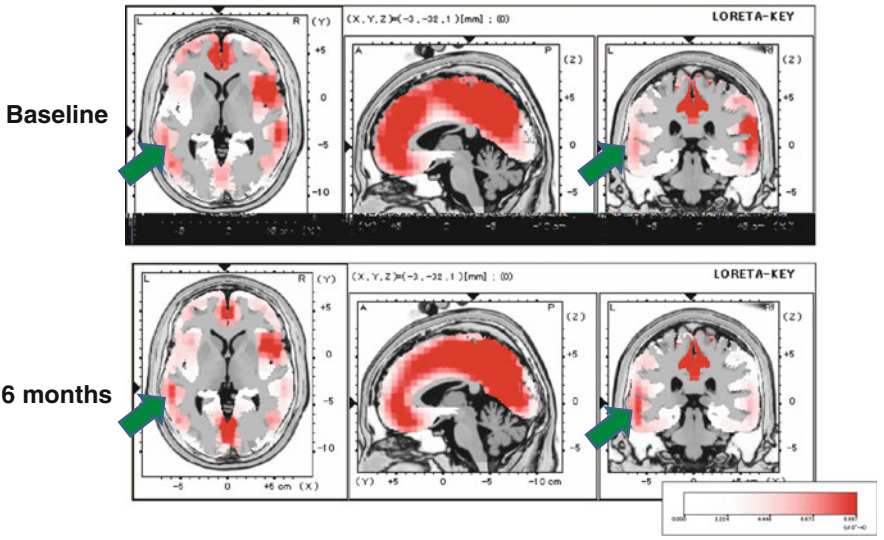

Fig. 7.6 LORETA images of P300; effect of olanzapine treatment. Six-month treatment with olanzapine enhanced P300 current source density in the left STG (indicated by *arrows*) [33]

density was noted, which is similar to the pattern of healthy controls [33, 44]. Moreover, significant correlations were noted between changes of verbal memory performance and LORETA values of the left STG, and between changes of quality of life and LORETA values of the left middle frontal gyrus (Fig. 7.7) [33]. These observations suggest that changes in cortical activity, as measured by EEG, are

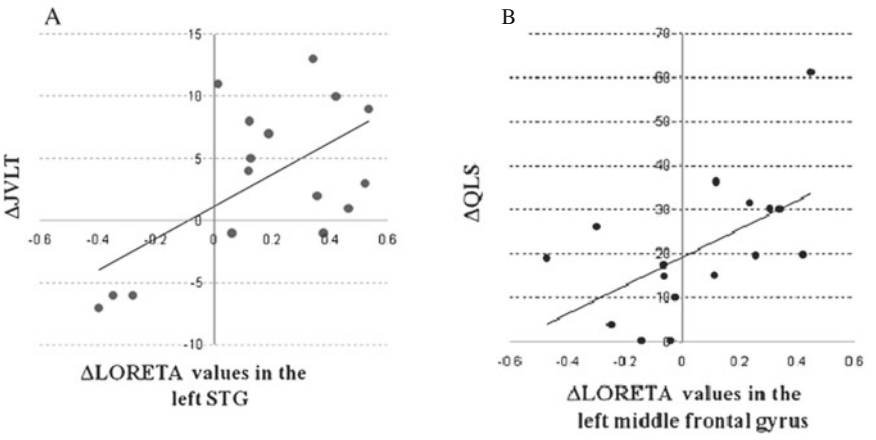

Fig. 7.7 (**A**) Changes in P300 current source density in the left STG by olanzapine were correlated with improvement in verbal memory, as measured by the Japanese Verbal learning Test (JVLT). (**B**) Changes in P300 current source density in the left middle frontal gyrus by olanzapine were correlated with improvement in quality of life, as measured by the Quality of Life Scale (QLS)

responsible for the ability of some antipsychotic drugs to improve cognitive and functional status in patients with schizophrenia.

From the clinical point of view, it is meaningful to examine the effect of type of antipsychotic drugs on the pattern of ERPs activation, as these compounds have been reported to possess differential profiles in terms of binding affinity for various neurotransmitter receptors [45]. Specifically, postmortem studies report that the serotonin-5-HT1A receptor density is increased in prefrontal cortical areas in subjects with schizophrenia [46, 47], suggesting altered 5-HT1A receptor-mediated transmission in this brain region [48, 49]. This concept is in agreement with clinical observations that augmentation therapy with 5-HT1A partial agonists, e.g. buspirone and tandospirone, enhanced the performance on some neuropsychological tests representing frontal lobe function in patients with schizophrenia [38, 50]. Therefore, it is conceivable that neural activity in frontal cortical regions would be enhanced by treatment with antipsychotic drugs with agonist actions at 5-HT1A receptors, such as perospirone [45], in patients with schizophrenia.

Using the same treatment paradigm as in the olanzapine study, above, we investigated the effect of perospirone on P300 current source density, as evaluated by the sLORETA method [4], in patients with schizophrenia, and examine the relationship between changes of P300 activity vs. performance on a cognitive task measuring the ability to evaluate component actions of social situations, which is related to frontal lobe function. As shown in Fig. 7.8 comparison of P300 current source density between baseline and 6-month after the start of treatment revealed a significantly enhanced neural activity in the left superior frontal gyrus, while conventional assessment of P300 amplitudes and latency were not significantly changed [51]. Some of the subjects studied here had been pre-treated with other antipsychotic drugs, including olanzapine, which are devoid of a noticeable affinity for 5-HT1A receptors. Therefore, our observations with perospirone provide further support to the

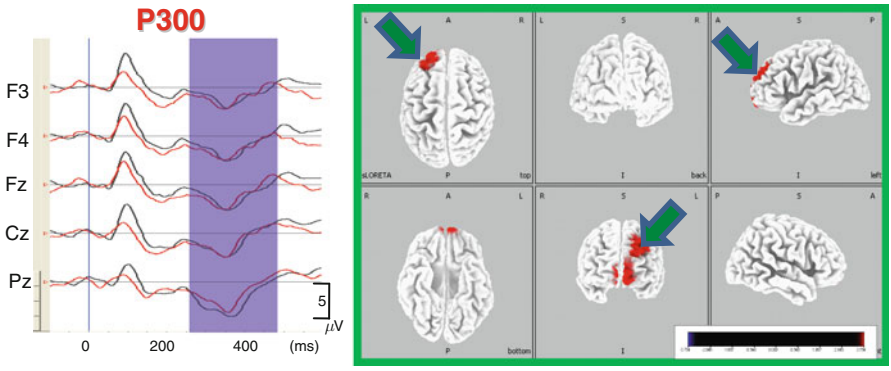

Fig. 7.8 Effect of perospirone on P300 current source density in patients with schizophrenia. Six-month treatment with perospirone enhanced P300 activity in the left superior frontal gyrus (comparison of P300 sLORETA values between before and after 6-month treatment) [51]

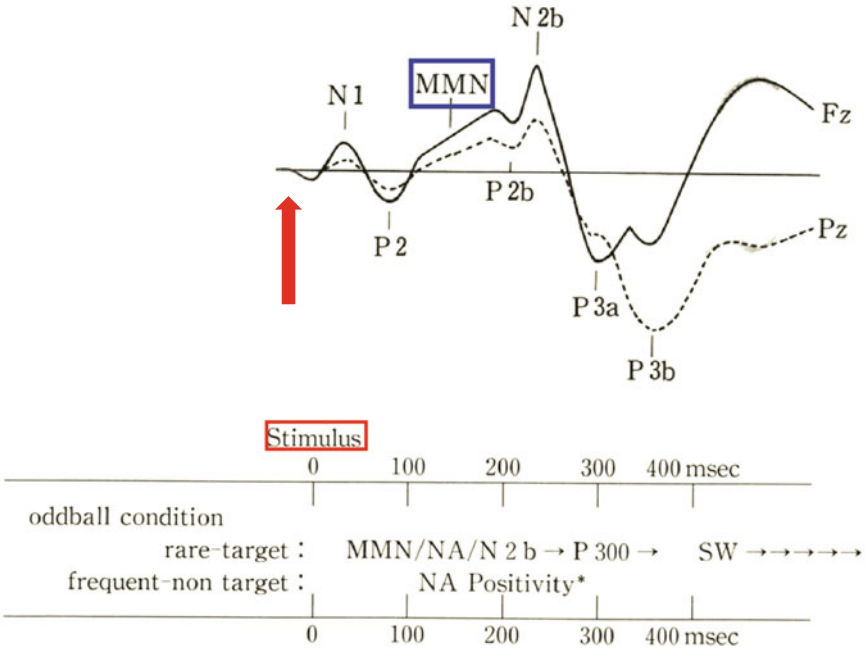

Fig. 7.9 ERP waveforms in response to the odd-ball tasks (rare-target)

concept that stimulation of 5-HT1A receptors may mediate the ability of this agent to increase P300 current source density in the left prefrontal cortex.

Mismatch negativity (MMN) is another component of ERPs generated in response to occasional variations of acoustic stimuli (Fig. 7.9) and is suggested to reflect *pre-attentive* cognitive operations [52]. We recently found the addition of tandospirone, a 5-HT1A partial agonist and anxiolytic [50, 53], was effective for enhancing MMN [54]. This is consistent with previous reports that 5-HT1A agonists, e.g., tandospirone [50, 53, 55], buspirone [38], and perospirone [51, 56], ameliorated cognitive deficits related to frontal and temporal lobe function in subjects with schizophrenia.

Conclusions and Future Directions

Neuroimaging of ERP components, such as P300 and MMN, are also expected to provide an objective diagnostic tool. We conducted discriminant function analysis of multivariate linear model using the statistical parametric mapping (SPM) in order to construct an optimal model to distinguish between healthy controls and patients with chronic schizophrenia [57] (Fig. 7.10). Although the classification power was not enough due, possibly, to the fact that these patients were mixed in terms of

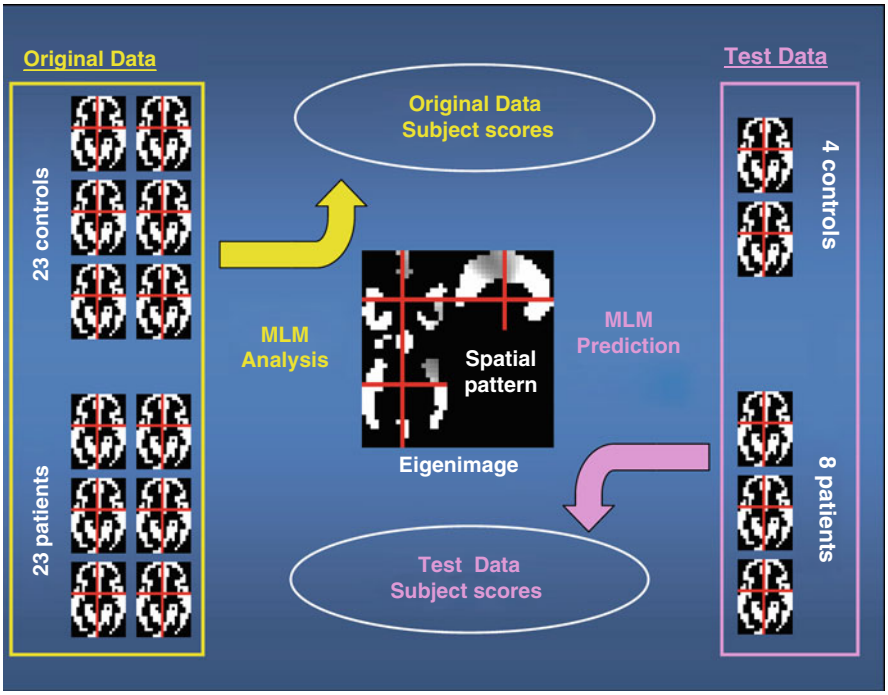

Fig. 7.10 The general scheme of discriminant function analysis of multivariate linear model (MLM) *using the* statistical parametric mapping [57]

treatment status [57], application of this method to drug-naïve subjects with first episode schizophrenia and those at the prodromal stage is likely to facilitate early intervention into the illness.

In conclusion, the utilization of neuroimaging methods enhances spatial resolution of electrophysiological evaluation, e.g. ERPs, which would provide feasible and reliable biomarkers, objective assessments of psychosis and cognition, and predictive measures of treatment response, and facilitate early diagnosis and intervention of schizophrenia.

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Chapter 8
Coping with Schizophrenia: Measuring Coping Styles, Patterns and Temporal Types

Michael S. Ritsner and Paul H. Lysaker

Abstract How persons prefer to cope with stressful life events play an important role in one's ability to adapt to stressful life conditions such as schizophrenia. Cross-sectional studies have shown that schizophrenia patients utilize several different (task-, emotion- and avoidance-oriented) coping strategies, both favorable and unfavorable, to cope with their disorder. Coping resources then come to play an important role in quality of life and outcomes of these patients. However, little is known about the long-term relationship between these psychosocial variables and coping patterns in schizophrenia. This chapter summarizes findings from three studies [18, 25, 26], which assessed the coping strategies of participants with schizophrenia and participants who did not suffer from any significant mental health condition using the Coping Inventory for Stressful Situations (CISS). Based on raw scores of task-, emotion- and avoidance-oriented coping strategies, eight CISS coping patterns were defined and four temporal coping types were distinguished (stable favorable and unfavorable, and becoming favorable and unfavorable). When eight CISS coping patterns were analyzed, the results revealed that schizophrenia patients used emotion related coping patterns 5.5 times more frequently, and task and task-avoidance coping patterns significantly less often than subjects without mental health conditions. Coping patterns had different associations with current levels of dysphoric mood and emotional distress, self-construct variables, and satisfaction with quality of life. In addition, coping patterns of 62.2% of schizophrenia patients remained stable over time, became unfavorable among 19.6% of patients, and became favorable among 18.2% of patients. Each temporal coping type is associated with a specific pattern of changes in clinical and psychosocial variables. The identified coping patterns and temporal coping types may illustrate the diversity of

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coping strategies used by schizophrenia patients and may be an important source of knowledge for patients who struggle with the illness and for mental health professionals who seek to assist them.

Keywords Coping · Schizophrenia · Exacerbation · Stabilization · Coping patterns · Changes in coping abilities · Self-esteem · Emotional distress · Symptoms · Quality of life

Abbreviations

BPRS	Brief psychiatric rating scale
CISS	Coping inventory for stressful situations
DSAS	Distress scale for adverse symptoms
GSES	General self-efficacy scale
HRQL	Health related quality of life
ITAQ	Insight and treatment attitudes questionnaire
MSPSS	Multidimensional scale of perceived social support
PANSS	Positive and negative syndrome scale
Q-LES-Q	Quality of life enjoyment and satisfaction questionnaire
RSES	Rosenberg self-esteem scale
TBDI	Talbieh brief distress inventory

Introduction

The ability to cope successfully with stressful situations and adverse life events is a key to adaptation for all human beings. The same is true for serious mental disorders such as schizophrenia. The extent to which persons can adaptively cope with the direct (e.g. symptoms) and indirect (e.g. stigma) consequences of schizophrenia plays a key role in whether persons can move towards health and recovery or remain in states of distress and dysfunction.

According to the cognitive-transactional theory of stress [1], coping has been defined as cognitive and behavioral efforts to manage the internal and external demands of a person-environment transaction that taxes or exceeds one's own resources. According to this theory, three main groups of coping strategies may be engaged in an individual's response to stressful situations including mental illness [2–4]. These include task-, emotion-, and avoidance-oriented strategies [3, 5]. Task-oriented coping is used to actively solve an underlying problem, cognitively reconceptualize it and potentially minimize its adverse effects. Deciding to change how one thinks about a conflict with a co-worker would be an example of task-oriented coping. Emotion-oriented coping strategies are person-oriented, and include emotional responses. In response to a conflict with a coworker an emotional focused coping strategy might be to decide to blame oneself. Avoidance-oriented coping involves both task and person orientations but also involves an attempt to put the stressor out of one's mind. For example one could respond to the stressor of

a conflict with a co-worker by drinking alcohol, seeking a diversion by going to a movie or trying to ignore that it ever happened. In addition to understanding coping as involving three broad classes of strategies, Lazarus and Folkman's [1] process-oriented coping model distinguishes between two major functions of coping: task- or problem-focused responses (aimed at altering person-environment relationships), and emotion-focused responses (aimed at regulating emotional distress).

To understand the widely varying courses that many with schizophrenia experience, research has focused increasingly on person centered factors such as coping styles, self-constructs, and temperament factors. In other words, health is not a matter of having or not having an illness but is closely tied in with how a person understands and responds to the challenges of the illness. Importantly such factors not only affect how the illness develops but also are affected by the illness itself. Mental disorders may themselves lead to potentially poorer ways of coping.

Regarding how persons with schizophrenia actually cope, cross-sectional studies have shown that both younger and older schizophrenia patients utilize several different strategies, both favorable and unfavorable, to cope with their disorder [6–11]. However, many with schizophrenia appear to be less flexible in their use of these coping strategies [12] and tend to use emotion-related or non-problem-focused coping strategies in response to stressors [10, 13, 14].

Regarding the consequences and antecedent of coping in schizophrenia, Wield [8] found that coping of schizophrenia patients with higher levels of negative symptoms in particular was characterized more often as emotion-oriented and less cognitive (task) oriented coping. This association becomes important to note since emotion-oriented coping is known to be associated with emotional distress, anxiety and depressive symptoms [13, 15–17]. Boschi et al. [11] found that after first hospitalization, individuals with more severe symptoms, as measured by the Brief Psychiatric Rating Scale (BPRS), tended to endorse a greater number of coping strategies, suggesting that employment of additional strategies may be a response to more severe symptomatology.

Avoidance-oriented coping strategies (distraction type) were found to be significantly and negatively correlated with paranoid symptom clusters. Levels of emotional distress, self-efficacy, and social support predicted coping strategies used by patients at the exacerbation and stabilization phases of schizophrenia, while severity of symptoms accounted only for 3.5% and 5.5–9% of the total variance of emotion- and task-oriented coping strategies, respectively [18]. Another study found that maladaptive coping strategies and trait negative affectivity in schizophrenia were associated with individual emotional responses to psychosocial stressors [14]. One possibility offered by Aldebot, de Mamani [19] is that a tendency to deny stressors leads to lower rates of adherence which then leads to heightened symptoms. Beyond symptoms, coping resources may also play an important role in health related quality of life (HRQL) outcomes of schizophrenia patients [15, 20–24]. Emotion-oriented coping has been found to mediate the relationship between the severity of the Positive and Negative Syndrome Scale (PANSS) activation symptoms, anxiety and depression symptoms, and HRQL, while avoidance coping mediated the relationships between paranoid symptoms and HRQL [15].

In summary research has suggested that many with schizophrenia struggle to cope effectively and that less adaptive coping is related to a range of more severe symptoms and decrements in quality of life. While this work offers us a promising window into understanding the variables which influence the course of illness several questions remain unaddressed. First, since most of the literature to date has been cross sectional it is unclear whether there are differences in task, avoidance and emotion-oriented coping strategies of schizophrenia patients over time and whether those differences are linked to other person centered variables. Second, since most research on coping in schizophrenia has tended to focus on either individual pieces of the coping process or on general patterns of active vs. passive or emotional focused approaches to stressors, little is known about the effects of larger profiles of coping preference. Third, it is unclear whether coping styles that are more stable or less variable over time are more or less closely related to assessments of daily functioning.

To address these questions we will summarize three studies. The first examines differences in coping between patients with schizophrenia and persons without a psychiatric illness [25], the second explores differences in coping and related functional outcome in acute and post acute phases of illness [18], and the third reports on patterns of change and stability in coping strategies and their associations with psychosocial function and symptoms [26].

Study 1: Coping Styles Among Persons with Schizophrenia: Associations with Outcome

In the first study we will present, the aim was to determine how many main coping strategies influence the coping abilities of schizophrenia patients and healthy subjects. For instance, is there a substantial correlation between three main coping strategies and the defined coping patterns? Do schizophrenia patients tend to use different coping patterns than healthy individuals? In addition, we sought to determine what clinical and psychosocial factors are associated with coping patterns used by schizophrenia patients. To examine this issue we began with three a priori hypotheses: Correlation coefficients between main coping strategy scores would not reach significant levels among patients with single and binary coping patterns; patients with schizophrenia substantially differ from healthy individuals in the rate of use of coping patterns; and various coping patterns are differentially associated with clinical and psychosocial variables.

Participants included a total of 237 patients, 176 who presented with paranoid type, 38 with residual type, 11 with disorganized type, 11 with undifferentiated type, and 1 with catatonic type. Overall, 128 (54%) patients received only first generation and 75 (31.6%) only second generation 31 (13.0%) antipsychotics and 28 (11.8%) received both types (6 or 2.5% of the patients did not receive any antipsychotic agents). In addition, several patients received concomitant medications (36% benzodiazepines, 17% antidepressants, and 10% mood stabilizers) as clinically indicated.

The non-patient group included 175 healthy subjects from auxiliary hospital staff members excluding physicians (inclusion based on interview availability). They had no known psychiatric history and did not meet DSM-IV criteria for any mental disorder. The demographics of both groups are presented in Table 8.1.

After diagnosis was assessed with face-to-face interview and consensus between two psychiatrists, **c**oping for all participants was measured using the Coping Inventory for Stressful Situations (CISS) [3]. This CISS consists of 48 statements concerning ways in which people could react to various difficult, stressful, or upsetting situations. The items can be grouped into three 16-item orthogonal factors of

Table 8.1 Sociodemographic and illness characteristics of the initial and follow up samples of schizophrenia patients

	Initial sample ($N = 237$)		Follow-up sample[c] ($N = 148$)	
Characteristic	Mean	SD	Mean	SD
Male, *N* (%)	188	(79.3%)	121	(81.8%)
Marital status, *N* (%)				
Single	150	(63.3%)	97	(65.5%)
Married	44	(18.6%)	25	(16.9%)
Other[a]	43	(18.1%)	26	(17.6%)
Age at examination, yr.	37.9	9.9	38.2	9.5
Education, yr.	10.2	2.8	10.2	2.7
Age of onset[b], yr.	23.4	7.8	22.9	7.1
Illness duration, yr.	14.3	9.4	15.0	9.1
Total number of hospitalizations	7.6	4.6	7.8	4.5
Paranoid subtype of illness	176	(73.4%)	104	(70.2%)
PANSS, total	84.3	19.5	82.3	20.8
Negative	30.0	8.5	30.8	9.2
Positive	12.4	4.7	11.1	4.5**
Activation	14.8	4.4	13.7	4.4*
Dysphoric mood	11.4	3.9	9.7	3.4***
Autistic preoccupation	19.1	5.2	19.6	5.6
Emotional distress (TBDI)	1.3	0.8	1.1	0.8**
Insight (ITAQ)	12.6	6.5	15.0	6.9***
Self-efficacy (GSES)	27.3	8.0	28.6	8.3
Self-esteem (RSES)	18.1	4.8	19.1	5.1
Social support (MSPSS)	55.4	17.8	59.9	17.2*
Quality of life (Q-LES-Q), general index	3.4	0.7	3.5	0.8

[a]Widowed or divorced

[b]As per age of initial mental health care referral

[c]Two-tailed *t*-test (df = 383): $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

PANSS higher ratings indicate a severe psychopathology, *TBDI* scores range between 0 and 4; higher scores indicate a severe emotional distress, *ITAQ* scores range between 10 and 40; higher scores indicate a higher self-efficacy, *GSES* scores range between 10 and 40; higher scores indicate a higher self-efficacy, *RSES* scores range between 10 and 40; higher ratings indicate a higher self-esteem, *MSPSS* scores range between 12 and 84; higher ratings indicate a higher perceived social support, *Q-LES-Q* scores range between 1 and 5; higher ratings indicate a higher satisfaction with life quality

task-oriented (T) coping (e.g., Think about how I have solved similar problems or Analyze the problem before reacting), emotion-oriented (E) coping (e.g., Tell myself it is not really happening to me, or Blame myself for not knowing what to do), and avoidance-oriented (A) coping. Participants were asked to indicate how often they currently used each of the 48 coping strategies on a 5-point scale ranging from 1 (not at all) to 5 (very much).

Concerning patients only, we assessed symptoms using the Positive and Negative Syndrome Scale (PANSS) [27] and utilized a five factor model which yielded scores for: positive, negative, activation, dysphoric mood and autistic preoccupation [28]. The presence and severity of adverse (or side) effects of medication as well as psychological responses to them were measured with the Distress Scale for Adverse Symptoms (DSAS) [22]. To assess distress we employed the Talbieh Brief Distress Inventory (TBDI) [29, 30]. The General Self-Efficacy Scale (GSES) [31] was used to assess sense of personal competence in stressful situations and the Rosenberg Self-Esteem scale (RSES) [32] was used to assess self-esteem and self-regard. The Multidimensional Scale of Perceived Social Support (MSPSS) was used as a measure of a social support [33]. Quality of life was assessed using the general index from Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [34].

To analyze the data, we first sought to identify the main factors associated with the 48 items of the CISS, through an exploratory factor analysis (see Table 8.2). Among schizophrenia patients three factors were identified on the highest eigenvalues: task coping related items, emotion coping related items and avoidance coping style. Eigenvalues were 9.15, 4.99, and 4.94 (7.67, 6.54 and 6.06 for healthy subjects), respectively. Correspondingly, these factors accounted for 46.9, 25.6, and 25.3% of the total variable among patients.

When we compared the mean scores of the three CISS coping dimensions of controls and schizophrenia patients, we found that the emotion oriented coping style was significantly higher in the schizophrenia group, whereas the task oriented coping style was lower compared with controls (Table 8.3). No statistical difference between the groups was revealed for the avoidance oriented coping style. ANCOVA indicated that between-group differences in emotion coping style scores appear to be associated with between-group differences in emotional distress, whereas between-group differences in avoidance coping style scores were related to self-efficacy and quality of life. Self-esteem and social support scores did not associate with between-group differences in coping styles. Between-group differences in task oriented coping style scores were unrelated to the covariates tested.

To increase accuracy, analysis of coping patterns as combinations of the three coping styles or dimensions were defined. Median scores obtained from the distributions of healthy subjects were used as cut-off points to split task-, emotion- and avoidance- oriented coping style scores into the two levels: high and low. Thus, the cut-off point scores on task-, emotion- and avoidance-oriented coping subscales were 64, 35 and 48, respectively. The scores higher than median reflect the participant's coping pattern that may include one, two or all three coping strategies. For example, the combination of high task- and high emotion-oriented copings with low avoidance-oriented coping is defined as TE coping pattern. Using this

Table 8.2 Factor analysis for CISS items among 237 schizophrenia patients

	Factor loadings after varimax rotation			Communalities after varimax rotation		
CISS items	Factor2	Factor2	Factor3	Factor1	Factor2	Factor3
1.	**–0.5970**	0.0444	0.2246	0.3564	0.0019	0.0504
2.	**–0.6717**	–0.0094	0.1540	0.4512	0.0001	0.0237
3.	–0.2981	–0.1028	**0.4337**	0.1585	0.0105	0.2881
4.	–0.2907	0.0429	**0.4249**	0.0845	0.0018	0.2805
5.	–0.2990	**–0.4036**	0.0843	0.0894	0.2308	0.0071
6.	**–0.5533**	0.0563	0.2658	0.3062	0.0031	0.0707
7.	–0.0397	**–0.5481**	0.1740	0.0015	0.3004	0.0302
8.	–0.1562	**–0.6093**	0.0904	0.0244	0.3713	0.0081
9.	–0.2032	–0.2277	**0.4177**	0.0412	0.0518	0.2009
10.	**–0.6497**	–0.0042	0.2219	0.4221	0.0000	0.0492
11.	–0.1550	–0.2918	**0.4001**	0.0240	0.0851	0.1841
12.	–0.1485	–0.1584	**0.5770**	0.0220	0.0250	0.3329
13.	0.0674	**–0.6422**	0.0152	0.0045	0.4124	0.0002
14.	0.1427	**–0.7589**	–0.0277	0.0203	0.5760	0.0007
15.	**–0.5382**	–0.1050	0.1871	0.2896	0.0110	0.0350
16.	–0.2384	**–0.4709**	0.3060	0.0568	0.3734	0.0936
17.	–0.2035	**–0.6565**	0.0758	0.0414	0.4310	0.0057
18.	–0.2256	–0.0919	**0.5935**	0.0509	0.0084	0.3522
19.	0.0732	**–0.6887**	–0.1552	0.0053	0.4743	0.0240
20.	–0.2244	–0.0727	**0.5569**	0.0503	0.0052	0.3101
21.	**–0.6046**	–0.1306	0.1038	0.3655	0.0170	0.0107
22.	–0.1673	**–0.6971**	–0.0094	0.0280	0.4859	0.0001
23.	–0.2768	0.1473	**0.5226**	0.0766	0.0217	0.3732
24.	**–0.6210**	–0.1684	0.1609	0.3857	0.0283	0.0258
25.	0.0151	**–0.5173**	–0.0060	0.0002	0.2676	0.0000
26.	**–0.6806**	0.0021	0.1503	0.4632	0.0000	0.0226
27.	**–0.6709**	–0.1178	0.1724	0.4501	0.0138	0.0297
28.	–0.2800	**–0.5121**	0.1884	0.0601	0.2695	0.0355
29.	–0.2459	0.0496	**0.5622**	0.0604	0.0024	0.3161
30.	–0.3083	**–0.4483**	0.1315	0.0950	0.2010	0.0172
31.	–0.0623	–0.0738	**0.4461**	0.0038	0.0054	0.1990
32.	–0.3746	–0.07169	**0.4936**	0.1403	0.0051	0.2549
33.	–0.1784	**–0.4588**	0.3082	0.1289	0.3670	0.0950
34.	–0.0738	**–0.4407**	0.1897	0.0245	0.3161	0.0359
35.	–0.1806	–0.1585	**0.4280**	0.1310	0.0251	0.2832
36.	**–0.6895**	–0.0106	0.2273	0.4754	0.0001	0.0516
37.	–0.2797	0.0184	**0.5543**	0.0782	0.0003	0.3073
38.	0.0131	**–0.6307**	–0.0217	0.0001	0.3977	0.0004
39.	**–0.6711**	–0.0199	0.2552	0.4504	0.0003	0.0651
40.	–0.2079	–0.0765	**0.5712**	0.0432	0.0058	0.3262
41.	**–0.7173**	0.1305	0.3054	0.5145	0.0170	0.0932
42.	**–0.7297**	–0.1116	0.2356	0.5325	0.0124	0.0555
43.	**–0.6537**	–0.1563	0.2149	0.4273	0.0244	0.0462
44.	–0.2315	–0.2611	**0.5559**	0.1304	0.0682	0.5565
45.	–0.0688	**–0.4806**	0.1971	0.0047	0.1448	0.0388
46.	**–0.5206**	–0.0515	0.3528	0.2711	0.0026	0.1244
47.	**–0.7114**	–0.0020	0.2332	0.5061	0.0000	0.0544
48.	–0.1763	–0.0277	**0.6076**	0.0311	0.0007	0.3691

Variables with an absolute loading greater than the amount set in the minimum loading option (>0.4) were selected (bold).

Table 8.3 Comparison of coping style scores between 237 schizophrenia patients and 175 healthy subjects

	Schizophrenia patients		Healthy subjects		ANCOVA[a]		Emotional distress[b]		Self-efficacy[c]		Self-esteem[d]		Social support[e]		Quality of Life[f]	
CISS dimensions	*M*	SE	*M*	SE	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Task coping	50.4	0.9	62.4	1.1	39.6	0.001	28.7	0.001	6.7	0.01	71.0	0.001	35.7	0.001	14.4	0.001
Emotion coping	43.6	0.8	36.0	1.0	19.2	0.001	0.08	0.78	12.5	0.001	36.8	0.001	23.4	0.001	8.9	0.003
Avoidance coping	47.2	0.9	48.2	1.1	0.3	0.61	0.01	0.99	6.2	0.013	0.8	0.14	1.8	0.64	4.6	0.003

Means and standard errors (SE) are shown

[a]Two-way ANCOVA: 1st factor- being schizophrenia patients or healthy subject (df = 1412), 2nd factor – sex (df = 1412) with controlling for age (years) and education (years). Additional covariates (scores)

[b]The Talbieh Brief Distress Inventory

[c]The General Self-Efficacy Scale (patients: 49.5 ± 0.9, controls: 45.2 ± 1.0)

[d]The Rosenberg Self-Esteem scale

[e]The Multidimensional Scale of Perceived Social Support

[f]The Quality of Life Enjoyment and Satisfaction Questionnaire (patients: 49.1 ± 0.9, controls: 45.4 ± 1.0)

method, apart from the pure coping styles (T, E, and A-oriented) we identified the following pairs of coping patterns: task-emotion (TE), task avoidance (TA), and emotion-avoidance (EA) patterns. In addition, there were triplet combinations of all coping styles: task-emotion-avoidance-oriented (TEA) at two levels: higher and lower than median score (h-TEA and l-TEA, respectively). Mean scores of task-, emotion- and avoidance oriented coping strategies were evaluated among patients across coping patterns as depicted in Fig. 8.1. As can be noted, patients with T- and TE-coping patterns showed higher scores on the task oriented coping subscale. Patients who used A-, TA-, h-TEA- and l-TEA patterns reported higher scores on task and avoidance coping subscale, while patients with E and EA coping patterns scored similarly on three CISS subscales.

Concerning the frequencies of the coping patterns patients with schizophrenia used the E-oriented coping pattern 5.5 times more often than the non-patients. By contrast, patients used T- and TA coping patterns less frequently than non-patients (Odds ratio = 0.2–0.4). The patients and non-patients did not differ in the frequency of the use of A, TE, EA and coping triplets (TEA) at both high and low levels. Concerning the correlates of the eight coping patters within the schizophrenia group. Using ANOVA we found a significant association of coping patterns with dysphoric mood ($F = 5.1$, df = 7237, $p < 0.001$; but not with other symptoms), emotional distress ($F = 6.8$, df = 7237, $p < 0.001$), quality of life ($LF = 7.6$, df = 7, $p < 0.001$), self-efficacy ($F = 13.5$, df = 7237, $p < .001$), self-esteem ($F = 9.2$, df = 7237, $p < 0.001$) and perceived social support ($F = 4.4$, df = 7237, $p < 0.001$). The coping patterns were not associated with gender, marital

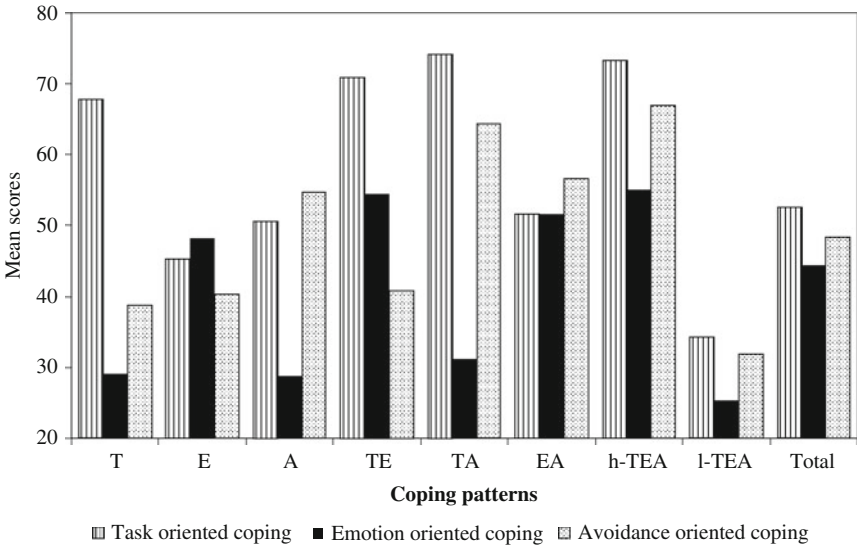

Fig. 8.1 Mean scores of task-, emotion- and avoidance oriented coping strategies across coping patterns among 237 schizophrenia patients

status, living arrangement, employment status, treatment settings, age education, hospitalization or illness duration.

Results of this study were interpreted as suggesting that patients used emotion coping patterns more frequently, and task and task-avoidance coping patterns significantly less often than healthy subjects. Furthermore the degree to which persons use less adaptive coping patterns may be linked with greater levels of dysphoric mood and emotional distress, and poor self-concept as well as lower satisfaction with quality of life.

Study 2: Coping Patterns Across Acute and Post Acute Phases of Illness

In the second study [18] we will present, the aim was to explore whether there are differences in task-, avoidance-, and emotion-oriented coping strategies of patients with schizophrenia when assessed during acute and post acute stages of illness. For instance, are there differences at these various stages of the illness? In addition, we sought to explore to what extent clinical and psychosocial factors are associated with task-, avoidance-, and emotion-oriented coping strategies of patients with schizophrenia.

Participants were 237 patients with schizophrenia initially assessed on admission (closed, open, and rehabilitation hospital settings). Of those, 148 were then reassessed 12 months later while in a post acute stage of illness. Post acute or stabilization was defined as having no score on the PANSS of greater than "4". Demographic information is presented in Table x. In terms of socio-demographic and clinical characteristics (age, sex, diagnosis, age of onset, number of hospitalizations, and symptom severity), there were no significant differences between the follow-up sample and patients that were not followed up. Of a total of 237 patients, 176 presented with paranoid type, 38 with residual type, 11 with disorganized type, 11 with undifferentiated type, and 1 with catatonic type. Overall, 128 (54%) patients received only typical and 75 (31.6%) only atypical antipsychotics and 28 (11.8%) received both types 6 (2.5%) of the patients did not receive any antipsychotic agents. In addition, several patients received concomitant medications (36% benzodiazepines, 17% antidepressants, and 10% mood stabilizers).

After diagnosis was assessed through consensus following interview, **c**oping was measured using the CISS. As in the first study, we assessed symptoms using the PANSS and utilized a five factor model which yielded scores for: positive, negative, activation, dysphoric mood and autistic preoccupation [28]. The presence and severity of adverse (or side) effects of medication as well as psychological responses to them were measured with the DSAS. To assess stress processes, we employed the TBDI, GSES, RSES, MSPSS, and the general index from Q-LES-Q. Insight was assessed using the Insight and Treatment Attitudes Questionnaire (ITAQ) [35].

As reflected in Table 8.1, we found, a reduction in severity of positive ($p < 0.01$), activation ($p < 0.05$), dysphoric mood ($p < 0.001$) symptoms, and emotional distress ($p < 0.01$), from time one to time two (exacerbation and stabilization). At the

same time, the patients recorded improvement in insight into illness ($p < 0.001$) and perceived social support ($p < 0.05$). When repeated measures were compared with paired t test for the 148 followed up patients, significant improvement over time was noted in self-efficacy ($t = 2.1$, df = 148, $p = 0.034$), self-esteem ($t = 2.7$, df = 148, $p = 0.007$), and QOL ($t = 2.3$, df = 148, $p = 0.021$) scores.

A summary of multiple regression analyses of coping strategies at exacerbation and stabilization is presented in Table 8.4.

Concerning emotion-oriented coping, the best-fit data models explain 29–30% of the variability in emotion-related coping strategy scores at exacerbation and at stabilization (Table 8.4). Both models revealed 2 factors (emotional distress and social support) that positively associated with emotional coping. Specifically, emotional distress explains 29.3% of the variance in emotion-related coping at exacerbation compared with 18.9% at stabilization; contribution of social support is only 2.5–2.8%. Emotion-oriented coping strategy scores at the stabilization stage are also negatively associated with the following 4 variables: negative symptoms (3.9%), insight (4.1%), self-esteem (5.3%), and general Q-LES-Q index (7.0%).

Concerning task-oriented coping, regression analysis established a set of predictors that accounted for 38 and 47% of the total variance of the task coping scores at exacerbation and stabilization stages, respectively. The feeling of self-efficacy is a common positive predictor for both exacerbation and stabilization stages that account for 20.3 and 40.0% of variability of task coping scores, respectively (Table 8.4). Positive symptoms, side effects, and general Q-LES-Q index also positively related to task coping strategy at exacerbation. The data suggest that higher severity of activation (at exacerbation) and negative and autistic preoccupation (at stabilization) symptom scores were associated with lower task coping scores.

Concerning avoidance-oriented coping, regression analysis established a set of predictors that accounted for 32% of the total variance of the avoidance oriented coping at exacerbation and 42% at stabilization states (see Table 8.4). Self-efficacy, social support, and emotional distress showed markedly positive contributions to the prediction of avoidance coping strategy at both time points. Self-efficacy accounted for 11.9–15.0%, social support for 8.2–18.8%, and emotional distress for 3.6–7.1% of the total variance in avoidance coping strategy. Satisfaction with HRQL (at exacerbation) and lack of insight (at stabilization) are associated with a higher avoidance related coping strategy.

Finally, Table 8.5 presents changes over time in the 3 coping strategies. Here results indicated that emotion-oriented coping of patients decreased ($t = 2.3$, $p < 0.05$), whereas the task and avoidance coping strategies remained unchanged in magnitude. Regression analysis established the following sets of predictors that, overall, accounted (R^2) for 8, 21, and 17% of the total variance of the individual changes in emotion oriented and task- and avoidance-related coping strategy scores during the follow-up period, respectively (see Table 8.6). Particularly, increased self-efficacy scores were positively associated with coping abilities of each coping strategy; this accounted for 18.1% in increasing task-oriented, for 6.1% in avoidance-oriented, and for 2.7% in emotion-related coping scores. In addition, increased severity of self-report anxiety (TBDI) is associated with more use of

Table 8.4 Summary of multiple regression analyses to predict of coping styles at exacerbation and stabilization

Coping strategy	Independent variables	β	t-value	Partial R^2 (%)
Emotion related coping	*At exacerbation:* $R^2 = 0.29$, Adj. $R^2 = 0.29$, $F = 48.4$, df = 2237; $p < 0.001$			
	Emotional distress	0.57	9.8***	29.3
	Social support	0.14	2.4*	2.5
	At stabilization: $R^2 = 0.30$, Adj. $R^2 = 0.27$, $F = 10.1$, df = 6148; $p < 0.001$			
	Insight	–0.19	2.5*	4.1
	Negative factor	–0.18	2.4*	3.9
	Quality of life	–0.43	3.2***	7.0
	Emotional distress	0.71	5.7***	18.9
	Social support	0.17	2.0*	2.8
	Self-esteem	–0.30	2.8**	5.3
Task related coping	*At exacerbation:* $R^2 = 0.38$, Adj. $R^2 = 0.37$, $F = 28.4$, df = 5237, $p < 0.001$			
	Side effects[a]	0.18	3.2**	4.2
	Positive factor	0.17	2.9**	3.6
	Activation factor	–0.13	2.1*	1.9
	Quality of life, general index	0.17	2.6**	2.9
	Self-efficacy	0.48	7.7***	20.3
	At stabilization: $R^2 = 0.47$, Adj. $R^2 = 0.46$, $F = 42.4$, df = 3148; $p < 0.001$			
	Negative factor	–0.23	2.0*	2.8
	Autistic preoccupation	–0.36	3.1**	6.2
	Self-efficacy	0.61	9.8***	40.0
Avoidance related coping	*At exacerbation:* $R^2 = 0.32$, Adj. $R^2 = 0.32$, $F = 26.7$, df = 4237; $p < 0.001$			
	Quality of life, general index	0.18	2.4*	2.5
	Emotional distress	0.28	4.2***	7.1
	Self-efficacy	0.36	5.6***	11.9
	Social support	0.28	4.5***	8.2
	At stabilization: $R^2 = 0.42$, Adj. $R^2 = 0.41$, $F = 25.9$, df = 4148; $p < 0.001$			
	Insight	–0.17	2.5*	4.2
	Emotional distress	0.20	2.3*	3.6
	Self-efficacy	0.42	5.0***	15.0
	Social support	0.42	5.7***	18.8

Significance: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$
[a]Distress Scale for Adverse Symptoms (DSAS)

emotion-related coping, whereas reduction of autistic preoccupation and better social support are associated with increased task- and avoidance-related coping strategy scores, respectively.

We interpreted results as suggesting that the *experience of emotional distress, self-efficacy, and social support* appear to be the factors most associated with coping strategies both at exacerbation and stabilization phases of the illness. More

Table 8.5 Change in coping strategies among 148 schizophrenia patients during follow-up period (raw scores)

	At exacerbation	At stabilization	Differences	
Coping strategy	Mean ± SD	Mean ± SD	95% CI	Paired *t*-test*
Task oriented coping	51.7 16.8	51.6 17.7	–2.8 to 3.2	0.1
Emotion oriented coping	43.8 14.1	41.8 12.8	–4.6 to –0.1	2.3*
Avoidance oriented coping	47.8 14.2	47.2 15.9	–3.1 to 2.3	0.5

*Paired *t*-test (df = 148): $p < 0.05$

Table 8.6 Summary of multiple regression analyses to predict changing coping strategies over time from change of independent variables

Changing coping	Changing independent variables	β	*t*-value	Partial R^2 (%)
Emotional related coping	$R^2 = 0.08$, Adj. $R^2 = 0.07$, $F = 6.2$, df = 2148; $p = 0.002$			
	Emotional distress	0.27	3.3***	6.9
	Self-efficacy	0.16	2.0*	2.7
Task related coping	$R^2 = 0.21$, Adj. $R^2 = 0.20$, $F = 18.7$, df = 2148; $p < 0.001$			
	Autistic preoccupation	–0.15	2.0*	2.8
	Self-efficacy	0.41	5.6***	18.1
Avoidance related coping	$R^2 = 0.17$, Adj. $R^2 = 0.16$, $F = 14.9$, df = 2148; $p < 0.001$			
	Social support	0.29	3.7***	8.9
	Self-efficacy	0.24	3.0**	6.1

Significance: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

specifically, findings suggest that patients with schizophrenia in a post acute phase of illness show a reduction in severity of psychopathology and emotional distress, better insight into illness, self-efficacy, self-esteem, social support, and life satisfaction with HRQL. Although these particular findings are not unexpected, they do seem to indicate that during the stabilization period, patients with schizophrenia become less distressed by their illness. This is duly reflected in improved coping skills. Thus, patients with schizophrenia tended to use more emotional coping strategies at exacerbation, when they were more distressed, than in a post acute phase of illness while task- and avoidance oriented coping strategies remained unchanged in magnitude during the follow-up period.

Study 3: Pattern of Change and Stability in Coping Strategies Among Persons with Schizophrenia: Associations with Psychosocial Function and Symptoms

In the third study [26] we will present, the aim was to investigate changes in coping abilities over time. Specifically, we sought first to evaluate whether we could

identify specific coping styles across multiple assessment points. In other words we were interested in whether we could group participants according to coping style not as manifest in a single assessment but as manifest as a pattern across two assessments spanning 16 months, something which we will refer to as a temporal coping type. Second, we sought to explore the relationship of such temporal coping type with changes in clinical symptoms and psychosocial variables over time and thirdly were interested in assessing changes in psychopathology and psychosocial variables during the follow up period within patient subgroups with each temporal coping type.

The participants for this study were 148 patients initially in an inpatient status including 121 men and 27 women with mean age 38.2 years (SD = 9.5). Ninety-seven (65.5%) were single, 25 (16.9%) were married, and the remaining 26 (17.6%) were divorced, separated or widowed. Mean extent of education was 10.2 years (SD = 2.7); 84 (56.8%) lived independently, 43 (29.0%) in group homes and 21 (14.2%) with their families. Ninety-six patients (64.5%) were unemployed. Regarding diagnosis 104 patients presented with paranoid type, 27 with residual type, 8 with disorganized type, 8 with undifferentiated type, and 1 with catatonic type of schizophrenia.

To determine diagnosis a face-to-face interview, medical records, and a consensus between two senior psychiatrists was used. There after we performed two waves of assessments: one at baseline and one 16 months later. Coping was measured using the CISS. Coping patterns and modes were established as follows [36]: patient's task-, emotion- and avoidance oriented coping strategy scores were dichotomized into high and low according to median scores that were drawn from follow up data. The median score for task coping was 52, for emotion coping was 41, and for avoidance coping was 47. Scores of greater than median reflect a participant's preference for one, two or three coping strategies. Thus, the following coping patterns were identified: high only task (T), only emotion (E) or only avoidance (A); high task and emotion (TE), task and avoidance (TA), emotion and avoidance (EA) coping strategies; higher than medians in three coping strategies (h-TEA) and lower than medians in three coping strategies (l-TEA). Finally, on the basis of associations with clinical and outcome variables, these coping patterns were grouped into favorable (T, A, TE, TA, h-TEA) and unfavorable (E, EA, l-TEA) coping modes (Fig. 8.2).

To assess symptoms, we employed the PANSS and utilized a five factor model which yielded scores for: positive, negative, activation, dysphoric mood and autistic preoccupations. The presence and severity of adverse (or side) effects of medication as well as psychological responses to them were measured with the DSAS. To assess stress process we employed the TBDI, GSES, RSES, MSPSS, and the general index from Q-LES-Q.

Results of our analyses revealed that four temporal coping types could be distinguished based on trends of individual coping patterns from the baseline to follow up assessment (Fig. 8.2): (1) the "stable favourable" (SF) coping type characterizes stable favorable coping patterns, (2) the "stable unfavourable" (SU) coping type shows stable unfavorable coping patterns, (3) the "becoming favourable" (BF) coping

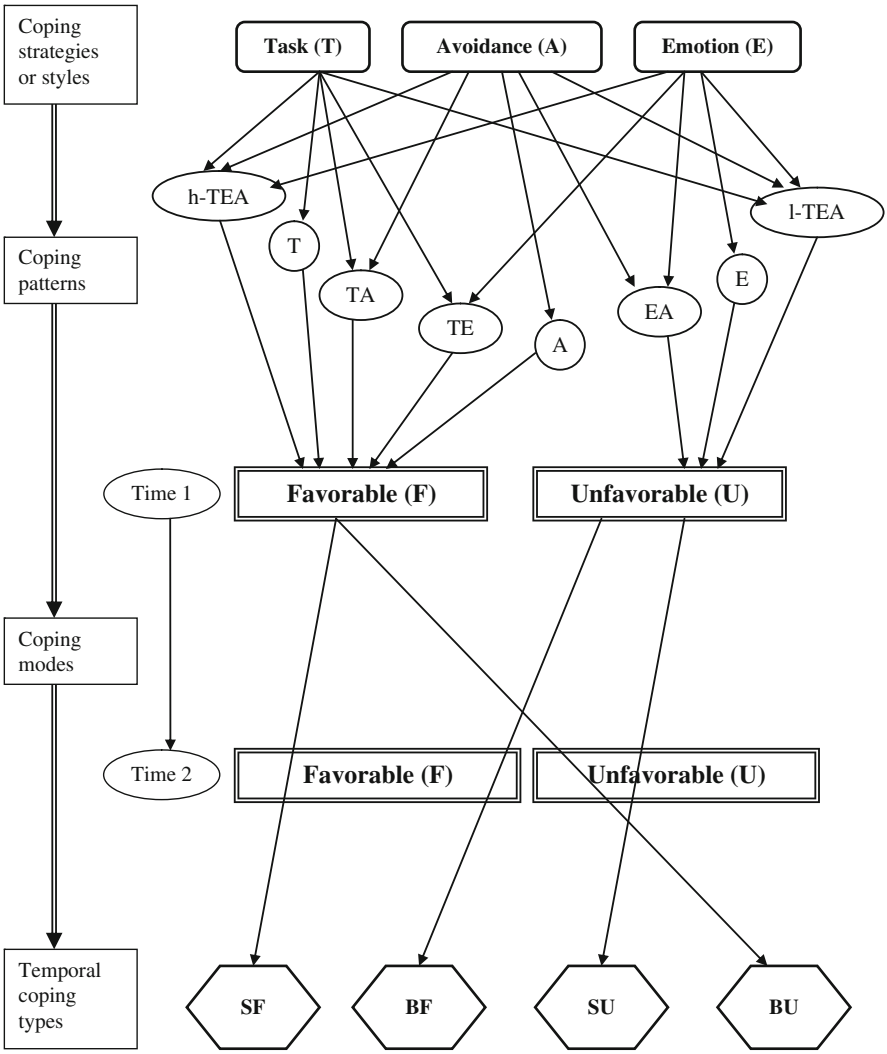

Fig. 8.2 Categorization of coping abilities in this study

type is characterized by improvement in coping abilities (unfavorable patterns were changed to favorable), and (4) the "becoming unfavourable" (BU) coping type displays worsening coping abilities (favorable patterns were changed to unfavorable). According to follow up data 148 patients were divided into the following groups: SF and SU coping types were found among 35.8% ($N = 53$) and 26.4% ($N = 39$) patients, respectively; BU coping type – 19.6% ($N = 29$), and BF coping type was observed among 18.2% ($N = 27$) patients. Temporal coping types were not related to age, gender, marital status, education, age of onset, number of hospitalizations, or illness duration.

Table 8.7 presents changes in specific coping patterns during the follow up period among patients in the BU and BF temporal coping types. As can be seen, at follow up examination 12 of 27 patients in the BF-group reported h-TEA pattern, 11 patients – TA or TE patterns, and 2 patients – T or A patterns. Contrarily, 16 of 29 patients of the BU-group were found with l-TEA pattern, 7 patients – with E and 6 patients – with EA coping patterns.

With regards to changes in symptoms and psychosocial variables over time, Table 8.8 presents initial and follow-up scores of key variables within each group of patients compared with paired *t*-tests. The becoming favorable coping type (BF group) was accompanied by a significant reduction of all symptom intensity, and improvement in other variables, except for side effects that remained on the former level. Patients in the stable favorable coping mode (SF group) significantly decreased severity of dysphoric mood and emotional distress, whereas the sense of self-esteem and social support increased. When the unfavorable coping mode was stable over time (SU group), clinical and psychosocial variables remained at the former level. Autistic preoccupation and self-efficacy worsened among subjects in the becoming unfavorable coping mode (BU group).

Between-group differences in changes over time in clinical symptoms and psychosocial variables associated with temporal coping types are presented in Table 8.9. Changes in negative symptoms and autistic preoccupation, emotional distress, self-efficacy, and HRQL were significantly associated with defined temporal coping types (MANOVA, Roy's Largest Root test, $F = 3.18$, df = 12,148,

Table 8.7 Change in coping patterns among patients getting favorable and unfavorable coping modes during follow up period

	Follow up assessment: becoming favorable coping type					
Initial assessment	T	A	TE	TA	h-TEA	Total
l-TEA	1	1	2	8	5	17
E	1	1	1	0	4	7
EA	0	0	0	0	3	3
Total	2	2	3	8	12	27
	Follow up assessment: becoming unfavorable coping type					
	l-TEA	E	EA	–	–	Total
T	2	1	0	–	–	3
A	5	1	2	–	–	8
TE	4	2	0	–	–	6
TA	1	0	0	–	–	1
h-TEA	4	3	4	–	–	11
Total	16	7	6	–	–	29

Coping patterns: task (T), emotion (E), avoidance (A), task-emotion (TE), task-avoidance (TA), emotion-avoidance (EA), higher than medians in three coping styles (h-TEA) and lower than medians in three coping styles (l-TEA)

Table 8.8 Change in mean scores of key variables between two examinations within group patients with various temporal coping types

	Becoming unfavorable coping type ($N = 29$)						Stable unfavorable coping type ($N = 39$)					
	Initial assessment		Follow up assessment		Paired *t*-test		Initial assessment		Follow up assessment		Paired *t*-test	
Variables	Mean	SD	Mean	SD	*t*	*p*	Mean	SD	Mean	SD	*t*	*p*
Negative symptoms	28.6	8.2	32.3	8.5	1.9	**0.054**	32.3	7.7	33.0	8.8	0.5	0.63
Positive symptoms	12.3	5.5	11.9	5.2	0.4	0.69	12.1	4.0	12.2	3.6	0.03	0.97
Activation symptoms	13.6	4.1	14.2	3.9	0.6	0.54	15.6	4.1	14.9	4.3	0.9	0.37
Dysphoric mood	12.1	4.2	11.1	3.8	1.1	0.29	11.9	3.6	10.7	3.0	2.0	**0.054**
Autistic preoccupation	19.4	5.2	21.7	5.0	2.3	**0.031**	20.4	4.3	21.5	4.6	1.2	0.25
Emotional distress	1.6	0.66	1.5	0.76	1.0	0.31	1.5	0.83	1.5	0.85	0.3	0.77
Self-efficacy	26.5	6.3	23.6	6.7	2.2	**0.038**	22.6	7.4	23.5	7.8	0.7	0.50
Self-esteem	17.1	4.4	17.1	4.7	0.1	0.97	15.8	4.6	16.3	4.1	0.6	0.53
Social support	56.0	16.8	51.9	16.9	0.9	0.33	49.8	17.8	50.7	16.2	0.2	0.81
Quality of life	3.2	0.64	3.1	0.69	0.2	0.80	2.9	0.64	2.9	0.65	0.4	0.66

Table 8.8 (continued)

	Stable favorable coping type ($N = 53$)						Becoming favorable coping type ($N = 27$)					
	Initial assessment		Follow up assessment		Paired *t*-test		Initial assessment		Follow up assessment		Paired *t*-test	
Variables	Mean	SD	Mean	SD	*t*	*p*	Mean	SD	Mean	SD	*t*	*p*
Negative symptoms	28.7	7.9	30.2	9.0	1.0	0.29	31.9	8.8	26.8	9.8	2.5	**0.019**
Positive symptoms	12.1	5.3	10.9	4.8	1.5	0.14	10.9	4.3	8.7	3.5	2.2	**0.038**
Activation symptoms	14.9	5.0	13.7	4.5	1.4	0.18	14.1	3.8	11.2	4.0	2.9	**0.007**
Dysphoric mood	10.7	4.0	9.1	3.2	2.4	**0.018**	10.2	3.4	7.9	2.7	2.4	**0.021**
Autistic preoccupation	18.2	5.0	18.3	5.4	0.2	0.87	19.6	5.5	16.7	6.1	2.1	**0.048**
Emotional distress	0.99	0.8	0.65	0.6	3.9	**0.001**	1.3	0.7	.83	0.7	3.4	**0.002**
Self-efficacy	31.8	6.7	33.6	6.3	1.5	0.14	24.5	8.2	31.3	6.4	4.0	**0.001**
Self-esteem	20.3	4.6	21.8	4.3	2.1	**0.038**	17.5	4.3	19.8	5.1	2.6	**0.015**
Social support	62.3	16.0	68.6	13.9	2.7	**0.009**	55.8	17.5	64.2	14.7	2.3	0.023
Quality of life	3.8	0.68	3.9	0.55	1.5	0.15	3.3	0.66	3.8	0.69	2.9	**0.007**

Variables with an absolute loading greater than the amount set in the minimum loading option (>0.4) were selected (bold).

Table 8.9 MANOVA for changes in key variables across four temporal coping modes[a] (Roy's Largest Root test, $F = 3.18$, df = 11,148, $p < 0.001$)

Change in variables	*F*-value (df = 3148)	*p*	Significant group differences ($p < 0.05$)[a,b]
Negative symptoms	3.93	0.009	BF>SU, BF>GU
Positive symptoms	0.99	0.40	Not significant
Activation	1.87	0.13	Not significant
Dysphoric mood	0.51	0.67	Not significant
Autistic preoccupation	3.49	0.017	BF>SU, BF>BU
Emotional distress	3.34	0.021	BF>BU
Self-efficacy	6.45	0.001	BF>SU, BF>BU; SF>SU, SF>BU
Self-esteem	1.45	0.23	Not significant
Social support	2.31	0.08	Not significant
Quality of life	2.72	0.045	BF>SU, BF>BU; SF>SU, SF>BU

[a]Group patients: SF = Stable favorable coping type ($N = 53$); SU = Stable unfavorable coping type ($N = 39$); BU = Becoming unfavorable coping type ($N = 29$); BF = Becoming favorable coping type ($N = 27$)

[b]Covarying for initial assessment of each variable; Tukey-Kramer Multiple-Comparison Test

$p < 0.001$). Patient groups with both favorable temporal coping types (stable or becoming) had significantly positive changes (improvements) in self-efficacy and quality of life outcomes compared to both patient groups with unfavorable temporal coping types (stable or becoming). The BF group also experienced negative symptoms and autistic preoccupation compared to patients in the SU and BU groups, and lower emotional distress levels than the BU-group.

Temporal coping types were also associated with changes in treatment settings during the follow up period ($\chi^2 = 21.3$, df = 6, $p = 0.002$). Specifically, 55.6% (15/27) of the patients with the BF coping type were discharged from hospital and reassessed in outpatient clinics, while 48.3% (14/29) of the BU-group patients were rehospitalized; 56.6% (30/53) patients with SF and 35.9% (14/39) – with SU temporal coping types remained in the same hospitalization and rehabilitation settings.

We interpreted results to suggest that (1) coping behavior of schizophrenia patients over time are characterized by four temporal coping types: both favorable and unfavorable coping types may be either stable or unstable over time; (2) for most patients coping style remained stable over time and each temporal coping type is associated with a specific pattern of changes in clinical and psychosocial variables.

Conclusions and Future Directions

This chapter has focused on three studies which have explored coping strategies among schizophrenia patients, specifically the stability of those strategies, changes

from acute to post acute phases and patterns of coping style over time, as well as the clinical and psychosocial correlates of each of the above.

As a summary of the implications of this work we offer the following:

- Patients with schizophrenia used emotion oriented coping patterns more frequently, and task and task-avoidance coping patterns significantly less often than healthy subjects.
- The degree to which persons use less adaptive coping patterns may be linked with greater levels of dysphoric mood and emotional distress, and poor self concept as well as lower satisfaction with quality of life.
- The experience of emotional distress, self-efficacy, and social support appear to be the factors most associated with coping strategies both at exacerbation and stabilization phases of the illness.
- Changes in coping over time appear to be linked to patients with schizophrenia becoming less distressed by their illness and finding a way to move towards recovery.
- When considered longitudinally, coping behavior of four temporal coping types characterize schizophrenia patients over time. Both favorable and unfavorable coping types may be either stable or over unstable with unfavorable coping at either point being linked to poorer function and life satisfaction.

One overall interpretation from the findings presented is that improved and more effective coping mechanisms may facilitate wellness of the resolution of the illness. It therefore follows that interventions by mental health caregivers should place emphasis in this domain as has been suggested in other conditions. For example, interventions intended to improve coping have been shown to enhance general problem solving [37], reduce pain and distress associated with medical illness and procedures (e.g. [38]) to increase treatment compliance [39]; and to improve adjustment to serious illness [40, 41]. Preliminarily, methods have been suggested which may facilitate such interventions including the importance of proactive coping [42], behavioral strategies [11], normalizing/optimistic systems [43] and meaning-based coping processes [44]. Others have also discussed how individual psychotherapy might assist some with schizophrenia to develop the capacity to engage in more complex self-reflection, a process likely to facilitate person's becoming better able to recognize what they are coping with, how they are coping and to assess the effectiveness of their coping [45, 46].

With regards to these methods, however, much remains to be studied regarding how change in coping style occurs and exactly what the barriers are to such change. For instance, as suggested by some [47], is that persons must first come to experience themselves as an active agent or possibly reject stigma before they can cope more effectively, or is it the other way around? Furthermore, is insight needed before persons can cope with their illness or do persons have to become able to effectively cope in general before they can acknowledge that they are ill and respond more adaptively to their psychiatric challenges? To what extent do deficits in neurocognition represent a barrier to improving coping? Lastly, analyses presented in

this chapter have looked at persons in general and outcomes in general. Thus it is unknown whether there are some for whom avoidant strategies are more effective and whether there are specific outcomes for which different forms of favorable and unfavorable coping are required (e.g. rejecting stigma vs. forming a new friendship).

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Chapter 9
Interventions Targeting Social and Vocational Dysfunction in Individuals with a Schizophrenia Spectrum Disorder

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Abstract Individuals with a schizophrenia spectrum disorder are among the most marginalized of any chronic illness group, having poorer performance and outcomes in nearly every domain of health and functioning. Poor social functioning is now widely acknowledged to be a major indicator of the prognosis of schizophrenia as well as a major contributor to illness outcome. Social and functional disabilities have serious detrimental effects on the individuals' quality of life and recovery, yet up until the twenty-first century treatment had largely been concentrated around symptomatic improvement, with the assumption that functional recovery would automatically follow. However, statistics on functional outcomes for individuals with schizophrenia and other psychotic illnesses suggest that this is in fact a relatively rare phenomenon. The definitions of "functioning" and "outcome" have also been poorly defined and inconsistent over the years, with alleviation of psychotic symptoms and decreased hospital admissions weighing heavily in the characterisation of improved functional outcome. In the last decade most studies have included a general measure of global functioning and/or education/employment as an indicator, but these performance measures have generally not been the primary topic of interest. Only recently has the incorporation of "social" functioning (i.e. social competence, independent living, community involvement and interpersonal relationships), been included as an important factor in overall outcome and moved into the spotlight as a major target for intervention. Historically, social skills training and cognitive remediation have been used to target deficits in social behaviour and cognition, respectively. However, new intervention strategies are being designed to target the underlying thinking patterns related to social interaction, termed social cognition. This chapter will review the different types of interventions that have been or are currently used to treat social and occupational

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dysfunction in schizophrenia spectrum illnesses, and assess their effectiveness in terms of the immediate and longitudinal outcome.

Keywords Illness outcome · Functional disability · Social functioning · Vocational intervention · Social cognition training · Early intervention

Abbreviations

ACC	Anterior cingulate cortex
CAT	Cognitive adaptation training
CBT	Cognitive behavioural therapy
CET	Cognitive enhancement therapy
CGI-CogS	Clinical global impression of cognition in schizophrenia
CRT	Cognitive remediation training
EMT	Emotion management training
EQ	Emotional intelligence/emotional quotient
EST	Enriched supportive therapy
FEP	First episode psychosis
GAF	Global assessment of functioning
HoNOS	Health of the nation outcome scale
ICCD	International Center for Clubhouse Development
IPS	Individual placement and support
MATRICS	Measurement and treatment research to improve cognition in schizophrenia
MCT	Metacognitive skills training
METT	Ekman's micro-expression training tool
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
NET	Neurocognitive enhancement therapy
NIMH	National Institute of Mental Health
PA	Picture arrangement
PACT	Program of assertive community treatment
POFA	Pictures of facial affect
QLS	Heinrichs-Carpenter quality of life scale
RCTs	Randomised controlled trials
SBS	Social behaviour schedule
SCET	Social cognition enhancement training
SCIT	Social cognition and interaction training
SF-36	36 item short-form health survey
SOFAS	Social and occupational functioning assessment scale
SOHO	Schizophrenia outpatients health outcomes
SSOS	Scottish schizophrenia outcomes study
SST	Social skills training
STS	Superior temporal sulcus
TAR	Training of affect recognition

TAU	Treatment as usual
ToM	Theory of mind
UCSD	University of California at San Diego
UHR	Ultra high-risk for psychosis
UPSA	UCSD performance-based skills assessment
WT	Work therapy

Introduction

Active psychosis is perceived as one of the three most disabling illnesses worldwide, ahead of paraplegia and blindness [1]. In 2006 the Prime Ministerial Science Engineering and Innovation Council of Australia highlighted that social and functional disabilities were two of the most concerning issues of psychosis, given they have serious detrimental effects on the individuals' quality of life and recovery [2]. In any 1 month, almost 50% of Australians suffering from schizophrenia are impaired in their ability to carry out normal routine activities of daily living [2]. In terms of relationships, approximately 70% of patients are never married and 59.4% have problems with socialising in general [3]. Moreover, as many as 70–92% are unemployed, which is more than any other disability group [2–6]. From a sample of over 1400 schizophrenia patients in the U.S., a similar percentage (72.9%) of patients were reportedly unemployed [7].

Among those patients who are experiencing their first episode of psychosis (FEP), the level of unemployment in Australia is also high, estimated to be 40–50% [5, 8, 9]. This compares to 10.9% (15–19 year olds) and 5.1% (20–24 year olds) of their same aged peers in the general community [10]. Despite the common misconception that individuals with FEP are not mentally fit for the workplace or are willing to work, the majority of patients do want to be employed in the open market [11].

Over and above the individual consequences of unemployment in psychosis, there are significant economic costs to the community. In Australia, costs associated with unemployment in individuals with schizophrenia equalled $927 million, of a total cost of illness of $1.85 billion in 2001 [6]. This included forgone salary, lost tax income and the costs of benefits payments. The costs associated with unemployment of people with schizophrenia have been found to be of similar magnitude in other countries and regions [12]. For example, in the USA, of the US$63 billion total national cost of schizophrenia, US$32 billion were associated with unemployment [13]. In the UK, the cost of schizophrenia on the economy in 2004/2005 was 6.7 billion pounds, from which 3.4 billion pounds was a result of lost productivity due to unemployment, absence from work and premature mortality [14]. Despite enhanced treatment efforts of recent years, it is now widely accepted that pharmacological treatment will generally have minimal secondary effects on social and occupational functioning. Given the persistent high cost of schizophrenia on the global economy, research has begun to focus on treatment targets that relate to constituents of functional outcome.

Defining "Functional Outcome" in Schizophrenia

Over the years, the term "illness outcome" has had many definitions and is often associated with the term "recovery". Previously, illness outcome typically referred to symptomatic improvement and reduced hospital admissions, suicide attempts and mortality rates. Today, in practical settings, illness outcome is often thought to represent all aspects of the disorder, including social and role functioning, especially considering impairment in functioning is a criteria for initial diagnosis of a schizophrenia spectrum disorder [15]. However, the criteria for illness "remission" (devised by the Remission in Schizophrenia Working Group), does not comprise a functioning dimension and is based on negative symptoms, disorganization and reality distortion [16]. While there is yet to be an operationalized definition of functional outcome, functioning has been described as "the performance of daily activities that are required for self-maintenance (earning an income and maintaining a residence), as well as social activities" [17]. Social functioning generally refers to a person's level of social competence, independent living, community involvement and interpersonal relationships. Occupational functioning typically refers to the amount of time spent in competitive or non-competitive (i.e. voluntary or transitional) employment and often includes job-seeking activities, school or tertiary studies and other roles such as home-maker (see Table 9.1 for definitions of key terms). Thus, the lack of consensus within the literature regarding a definition of functional outcome is due to the breadth of indices of functioning. This has lead to numerous types of measures being used to assess functioning, including: real-world milestones (such as independent living, employment etc.), interviewer-rated

Table 9.1 Definitions of key terms

Terminology	Definition
Functioning/functional outcome	The performance of daily activities that are required for self-maintenance (earning an income and maintaining a residence), as well as social activities (also referred to as social adjustment).
Disability	Involves dysfunction at one or more of the following levels: the body (including brain abnormalities, impairments in cognition and psychiatric phenomena); the person as a whole (difficulty executing activities); and the person in social contexts (participation restrictions).
Social functioning	A person's level of social competence, independent living, community involvement and interpersonal relationships.
Occupational functioning	The amount of time spent in a work role, includes competitive and non-competitive employment, job-seeking activities, school or tertiary studies and other roles such as home-maker.
Functional capacity	The ability or competence to perform everyday functioning skills (as can be measured in structured role-play assessments).

global assessment scales, third-party informant and self-report measures, and more recently role-play skill-based tasks. The many diverse constituents of functional outcome will be considered in this chapter. The challenges surrounding assessment of functioning will be discussed later in the context of future research directions.

While treatment of psychotic symptoms remains imperative, research has now begun to focus on how treatment can enhance functional outcome. This chapter will firstly provide an overview of the effects standard treatment has on functional outcome and the previous methods employed to address impaired social and occupational functioning. We will then review the link between social cognition and functional outcome and present findings on specific interventions aimed at directly or indirectly improving social and/or occupational functioning in schizophrenia spectrum disorders.

Effects of Standard Treatment on Functional Outcome

At present, data from numerous countries show that the functioning of individuals with a schizophrenia-spectrum disorder remains poor, despite being engaged in treatment services. A cross-national study in chronic schizophrenia outpatients from the U.S. (N=244) and Sweden (N = 146) who were currently receiving treatment, found approximately 80% were unemployed and approximately 60% had never been married. This was similar for both countries [18]. The percentage of patients who were living independently was less than 50% in the U.S., and approximately 80% for the Swedish cohort, which is considerably higher, likely due to the superior level of government-funded health care in Sweden. A naturalistic census-based survey in North London followed-up a sub-sample of 114 schizophrenia patients at 5 years [19]. Thirty-seven percent of patients were socially isolated (i.e. had not been in contact with friends in the previous month), 61% were living in supported or transitional housing and an astounding 99% were unemployed. Relationships with peers and living with family members were two of the best predictors of illness outcome at the 5-year follow-up. A retrospective audit conducted in a community-based psychiatric service in Melbourne assessed the effectiveness of 12 months assertive community treatment [20]. Authors found that although hospital admissions had decreased, overall levels of functioning remained extremely low, where 80% of patients were single or divorced, only 5% were living independently and 9% were currently employed.

Longitudinal and cross-sectional studies provide further evidence that standard treatment is largely ineffective for significantly improving functional outcome. Most longitudinal studies into psychotic disorders conducted in the last 10 years have included a general measure of global functioning (e.g. Global Assessment of Functioning [GAF] Scale [21], Social and Occupational Functioning Assessment Scale [SOFAS] [22]) and/or education/employment as an indicator of functional outcome. However, only modest improvements in functioning are observed longitudinally. Thus, functioning remains poor given that baseline levels are typically

characterised as major or serious impairment in several functional domains (e.g. SOFAS and GAF = ~40; Medical Outcomes Study-Short Form Health Survey [SF-36] [23] = ~30). A recent naturalistic multi-centre trial found that after an average of 67 days patients were discharged from hospital and only 20% met criteria for functional remission at that time, based on GAF, SOFAS and SF-36 scores [24].

The Schizophrenia Outpatients Health Outcomes (SOHO) study was an observational prospective 3-year study of 6642 participants who were recruited from 10 countries across Europe [25]. Long-lasting functional remission, defined as maintaining for at least 2 years: a positive role/vocational status (including paid or unpaid work, study or housewife activities), living independently and having active social interactions, was achieved by only 13% of patients. Again, social functioning at baseline was a significant predictor of long-term recovery.

The Scottish Schizophrenia Outcomes Study (SSOS) produced more promising results. Data was collected from a representative sample of 1015 individuals with a schizophrenia spectrum disorder, recruited via the Scottish National Health Service over 3 years. Although clinician-rated assessment (using the Health of the Nation Outcome Scale [HoNOS] [26]) suggested no change in behaviour and a decline in cognitive and physical impairment, there was a significant increase in social functioning according to the social problems subscales, based on personal relationships, overall functioning, residential and living conditions, and occupation and social activities [27]. At baseline approximately 5% of patients were engaged in the workforce (change in this measure over time was not reported). Scores on the self-report measure (Avon Mental Health Measure [28]) showed significant improvement overall, including social functioning, although improvement was modest (baseline M = 73.5, 24-months follow-up M = 75.4) and scores were still within the mid-range, implying optimal functioning had not yet been achieved.

Drug trials that included observer-rated functional assessment measures provide some limited support for positive treatment effects. Long-term treatment with the atypical antipsychotic ziprasidone was related to increased scores on the interpersonal subscale but not the role subscale of the Heinrichs-Carpenter Quality of Life Scale (QLS) [29, 30]. A similar 3-year trial found no significant change in mean GAF score for either the ziprasidone or haloperidol group [31]. Despite this, scores on the QLS gradually increased for the ziprasidone group over the 3 years, although this was partially mediated by symptomatology. An earlier study in less chronic patients (illness <5 years) also found only small improvements in functioning based in the QLS following 52 weeks of standardised atypical antipsychotic treatment (olanzapine, quetiapine or risperidone) [32].

A systematic review of research into early detection/intervention in FEP found 42% of patients had "good" illness outcomes as opposed to 27% who had "poor" outcomes at an average of 3 years follow-up [33]. In a recent 2-year follow-up study symptomatic remission was high among FEP patients, however functional remission (defined as SOFAS >60) was achieved by only 32.3% of subject, and of the 66 participants who dropped out after a minimum of 9 months, only 13% achieved good functional outcome [34]. However, a 1-year follow-up study in Ontario, Canada found better outcomes, with 51% of patients meeting this definition of functional

remission, in addition to 70% of patients reporting participation in work and/or school and satisfactory relationships [35]. Another naturalistic longitudinal study also found improved positive symptoms and social functioning (as measured by the QLS) after 3 years in a specialized first episode service, although negative symptoms persisted [36]. Similarly, randomized trials have shown intensive specialised treatment as opposed to standard treatment, to impact significantly on symptoms and admission rates at 2 years follow-up [37, 38]. This form of intensive "assertive outreach", which specifically involves such elements as extended service hours, tailored cognitive behavioural therapy (CBT), vocational therapy and family counselling, has also been shown to improve certain aspects of occupational/role functioning and relationships with family members/friends [39]. These findings lend support to early intervention strategies as key to the treatment and prevention of psychotic disorders. Accordingly, over the last 15 years there has been a move towards an early intervention approach, which has shown significant benefits over more traditional approaches to the treatment of psychotic illness [40]. Another review, which specifically focused on social, as well as role/occupational and community functioning, found long-term functional outcome to be poor for a substantial proportion of FEP patients [41]. Furthermore, two of the randomised trials mentioned above, failed to find intensive therapy to significantly influence the size of patients' social network [38, 39], or the amount of contact with existing friends [39]. In addition, although the later study found more patients in the intensive therapy group (49%) to have spent at least 6 months in educational/vocational activities, there remained to be a large percentage of patients who were considerably impaired in their role functioning at the 18-month follow-up. Overall, evidence suggests that the current biopsychosocial approach to treatment [42] is largely ineffective for the treatment of social and vocational impairment, highlighting the need for new interventions to specifically target social and occupational functioning.

Historical Approaches to Treatment of Social Disability

The 1970s heralded the emergence of social skills training (SST), which was developed based on social learning principles and driven by the desire to change abnormal or inappropriate behaviour. Techniques that form the core content of SST include immediate reward/reinforcement, observation of demonstrated behaviour, role-play, coaching, modelling, shaping, prompting and post-session practice exercises [43]. The effectiveness of such training for schizophrenia-spectrum disorders has been discussed previously in review articles [44–49] and meta-analyses [50–55], thus it will be reviewed only briefly here.

The UCLA Social and Independent Living Skills Program [56] was one of the most popular SST interventions during the late 1980s and 1990s. This was due to its highly instructive format that was readily available to clinicians. It addressed an array of topics in individualized modules, including: medication management, symptom management, recreation for leisure, basic conversational skills, substance

abuse management, workplace fundamentals and community re-entry [57]. A number of experimental studies have tested the effects of one or more of these modules on symptomatology and/or skill acquisition/social competence [58–64]. Several of these studies also investigated effects on functional outcome. Specifically, one study used the Social Adjustment Scale II [65] as an indication of overall functioning, which is a clinician rated semi-structured interview that assesses patients' level of involvement in various roles (e.g. work, household, family) and degree of engagement in social and leisure activities. The authors found long-term SST had modest positive effects on functioning over a control group supportive therapy program, however clinicians were not blind to treatment group, thus findings should be viewed with caution [63]. A study conducted in Beijing, China found social functioning, as assessed by the Chinese version of the Social Disability Screening Schedule, improved significantly for patients who received 8 weeks of SST based on the community re-entry module, in comparison to those who received supportive counselling [62]. In a more recent study Cirici et al. [58] used the Social Behaviour Assessment Schedule [66], an informant interview-based measure of social functioning, as well as a self-report measures to test the effects of 20 weeks SST in schizophrenia outpatients. According to informants (a relative or close friend) patients performed various social roles to a greater degree following treatment, for example being more talkative, friendly and interested in social and cultural events. In addition, patients also reported being more assertive following skills training. Overall, despite its popularity, rigorously controlled research into the effects of this SST program on functional outcome in schizophrenia populations is limited.

The major limitation of SST is that it focuses on teaching a specific set of behaviours based on the difficulties specified by the patient, such as difficulty finding a partner, or a specific area of disability such as medication management, therefore the social skills learnt will be somewhat inflexible and unsuitable for use in other social contexts. While efforts have been made to modify social skills programs to be more generalisable to every-day community living, by placing emphasis on rehearsal/reinforcement and providing out-of-clinic training sessions [64, 67, 68], the overall lack of robust effects on social and occupational functioning prompted researchers and clinicians to move away from this type of intervention strategy. A specific critique of randomised controlled trials concluded that such training does not provide "any benefits" for patients [51]. This caused heated debate, with the counter-argument being that there was insufficient empirical research to make such a conclusive remark [55]. Although the debate continues the most recent meta-analysis of RCTs supports SST as having moderate ($d = 0.52$) translational effects on community functioning (e.g. social relationships, community adjustment), although reportedly only seven of twenty-three studies assessed this domain [52]. Worth noting, effects of SST on measures of every-day living skills (mainly role-play tasks) were more pronounced during the early phase of the illness and when treatment duration was shorter [52]. In summary, social skills training has been successful in doing what it primarily set out to do – teach learned behavioural responses to social dilemmas/situations. However, in terms of overall social and occupational functioning this approach is often considered too narrow and outdated

in light of newer treatment strategies that aim to address the underlying thought processes that govern behaviour. Hence, the turn of the twentieth century marked the beginning of a dramatic rise in cognitive rehabilitative therapies.

There is an abundance of schizophrenia research demonstrating significantly improved cognitive performance on neuropsychological tests following repeated practice or strategy learning [44, 69–74]. However, it was not so long ago that the secondary effects of cognitive training, that is the influence on functional outcome, became a focus of clinical studies which have produced mixed results.

Several forms of cognitive remediation training (CRT) are therapist-driven (non computer-aided) interventions aimed at enhancing information processing strategies. One programme, developed in Australia [75, 76], has been repeatedly tested in RCTs [77–82]. However, none of these studies found significant group differences in social functioning measures, predominantly assessed with the informant-dependent social behaviour schedule (SBS) [83], when comparing the active CRT to TAU [79, 80, 82], or an intense occupational therapy program [77, 78, 81].

Cognitive Adaptation Training (CAT) takes a slightly different approach to traditional CRT programs and is a strategy most proximal to addressing real-world functional impairment. This form of therapy is manual-driven and uses compensatory environmental supports customised for the patient depending on their level of apathy, disinhibition and cognitive functioning. Therapy is conducted in patients' homes and uses tools such as signs, labels, checklists and electronic devices to cue and sequence appropriate behaviours, such as taking medication at a designated time. Consistent improvements in functioning, based predominantly on the SOFAS, have been observed with 3 months [84], 9 months [85–87] and 24 months [88] of CAT therapy when compared to a control group providing general environmental supports or TAU.

Training that is predominantly computer-based has also been a popular form of cognitive rehabilitation. A 3-month intensive domain-specific CRT program has been found to be superior to a control condition (computer aided non-domain-specific activity) in improving functioning, according to the QLS [89]. Dickinson et al. [90] however, failed to find a significant immediate or prolonged (3 months) effect of 15 weeks computer-assisted CRT on several functional outcome measures, including the University of California at San Diego (UCSD) Performance-Based Skills Assessment (UPSA) as well as another measure of social competence and a scale for rating participants' perception of cognitive effects on every-day functioning. Conversely, another computer-based educational cognitive therapy that focused specifically on problem solving was found to be more beneficial for patients' functional capacity than a memory training group or a control group [91]. However, the only outcome measures used were specific to problem solving abilities (authors factor analysed the Independent Living Scale [92] to produce a problem solving factor), although indicative of ability to cope with tasks of daily living. In line with these findings, Hodge et al. [93] found the Neuropsychological Educational Approach to Remediation [94] to be beneficial for occupational and social functioning (as measured by the SOFAS) after completion of the 10–15 weeks of training and at 4 months follow-up. However, other functioning measures (The World Health

Organization Quality of Life Scale-Brief Form and Life Skills Profile-39) did not change significantly.

A different treatment strategy that moves away from cognitive remediation and draws on principles from CBT is emotion management training (EMT) [95, 96]. This is a 12-week program that has three phases: (1) breaking down and analysing the emotional expressions displayed by others and the self, (2) review of current coping strategies and (3) development of new, "efficient" and appropriate coping strategies. Limited empirical research exists, however a small trial in 22 treatment-resistant schizophrenia patients found EMT in comparison to a problem solving group therapy, to significantly enhance performance on a facial emotion perception test and a measure of social adjustment [95]. After 4 months only the latter measure was significantly different between groups. An earlier pilot study that compared chronic patients to early psychosis patients has shown promising results, although documentation is lacking [96].

Recently, the schizophrenia Patient Outcomes Research Team decided not to recommend CRT as a psychosocial treatment for clinical practice based on a lack of consistent evidence supporting enhanced functioning [97]. Despite this they did acknowledge it as a growing area of interest that required further research. Like SST, there remains the issue of generalization, although some researchers argue that CRT which employs internal as opposed to environmental compensatory techniques is better equipped to address this issue [98]. However, this is only effective if the individual chooses to apply the learnt cognitive strategies in everyday situations. In addition to varying techniques and tools employed, the choice of functional outcome measures differed greatly between studies and may be a cause of mixed findings within the literature.

Past approaches to vocational interventions have included industrial therapy, social firms and clubhouse programs. Industrial therapy refers to the work tasks that were given to people in the old asylums. Often they were not remunerated, were not rehabilitative in focus and were open to exploitation by asylum managers [8]. Not surprisingly there was little evaluation of their effectiveness of helping people obtain competitive employment if and when they left the asylum.

Social firms were a European development. Social firms can be any type of business that provides a product or service to the public as a means of pursuing a social agenda [99]. In the Social Firms UK report it was found that 83% of social firms operated in the service sector [100]. While this was a small sample, in Italy, with over 5000 social firms 58% were in the service sector, 29% in the manufacture of handicrafts and the rest in areas described as building (4%), commercial (6%) and agricultural (3%) activities [101].

There has been little research on the effectiveness of social firms at helping people return to mainstream employment [8]. This is a great pity because the evidence from industry groups suggests this is a means by which people with mental illness could find work in an environment that is accommodating to the needs of their illness. There also seems to be longevity of employment. Tenure of employment is an area of vocational rehabilitation that has received less focus than it deserves in other forms of employment intervention. At the same time, social firms are not a modern

form of sheltered workshop. They are market-focussed businesses which choose to pursue a social outcome instead of a purely profit outcome.

The downside to social firms is that as with any business, a social firm requires a lot of time and energy just to establish, let alone run successfully. Further, having established a single social firm, it may not cater to the vocational needs of the individual. Therefore, what needs to be discussed in terms of social firms is not the establishment of one or two businesses, but the development of an employment sector.

The Clubhouse model was started by ex-psychiatric patients at Fountain House in New York in 1948. For the time, Fountain House had a radically rehabilitative approach towards mental illness in which it was posited that men and women with histories of mental illness could, through mutual support and encouragement, work productively and live socially satisfying lives [102]. Further, participants of Fountain House were members of a club (hence the clubhouse model) rather than patients and would work alongside a small generalist staff in the house as equals. At the club house, as well as having meaningful social encounters, a member contributes to the club by participating in voluntary work such as cleaning, clerical, research, hiring, training, public relations, and advocacy work for example [103]. The idea being that apart from contributing to the club the member develops some of the skills necessary to succeed in employment such as punctuality, confidence and responsibility. This is known as the Work Ordered Day [104]. Following on from this the person has access to a set period of employment in a local company. This transitional employment is central to the clubhouse model [105], and involves the club and the company making an arrangement whereby the company offers a number of positions which the job club guarantees to fill. The job club may then use 12 people, working part-time to fill four full-time positions. Each member would then typically receive 6–9 months of experience of employment in a real setting, for market or award wages. Since the mid 1990s the International Center for Clubhouse Development (ICCD), requires certified clubhouses to have access to a wide range of different employment settings in order to cater to the diversity of vocational interests that is likely to exist among their members. For example, Fountain House in New York placed 400 people at 41 different companies in 1998 including law firms, financial institutions and publishers [103]. Finally, at the end of this process it would be hoped that the member would be able to generalise the skills learned through the job club and transitional employment in order to obtain competitive employment [106]. However, because membership is for life, the individual can continue to contribute to the job club and use it as a place of socialisation and support. While this has been the traditional clubhouse model of employment (and clubhouses are still misrepresented as offering only transitional employment [107]), more recently clubhouses have viewed the work ordered day and transitional employment as the first two steps of a hierarchy of vocational interventions which continues on to supported employment and then independent employment [107]. In a worldwide survey of ICCD certified clubhouses in 2000 it was found that transitional employment provided 36.6% of job placements, supported employment 26.6% and independent employment 36.8% [107, 108]. The importance of accreditation was seen in a study in which Macias

et al. [109] compared 73 certified clubhouses with 48 non-certified clubhouses. While they found that both groups appeared organisationally similar and had similar resources, the certified clubhouses had a wider range of rehabilitative services and a better outcome in terms of members finding competitive employment [109].

The only study to date which actually compared ICCD certified clubhouses to another approach was reported by Macias [110]. This study compared the ICCD clubhouse intervention and the Program of Assertive Community Treatment (PACT). PACT is an intensive mobile treatment team providing clinical and rehabilitation services in the community [110]. The final sample consisted of 175 people and analyses were conducted on an intention-to-treat basis. Measurements were carried out at baseline, and 6, 12, 18 and 24 months. PACT and ICCD had similar outcomes on a number of measures including the number of participants who started competitive work, the number of participants interested in work at baseline who started competitive work, job satisfaction and the amount of time from enrolment until commencing work. The ICCD clubhouse performed better than PACT on measures of days worked, money earned, quality of jobs, hourly rate of pay, and job tenure. PACT performed better than the ICCD clubhouse on participant retention.

Social Cognition in Psychosis and Links to Functional Outcome

Social Cognitive Deficits are Widespread in Schizophrenia-Spectrum Disorders

Social cognition has been defined as the domain of cognition which involves the perception, interpretation and processing of social information [111]. Four key social cognitive abilities have been implicated in schizophrenia pathology: emotion perception (recognition of facial and vocal affect); social perception/knowledge; Theory of Mind (ToM; the mental capacity to infer one's own and others' mental states) and; attributional style (tendencies in explaining the cause of events, i.e., to the self, others or the environment) [112].

A substantial body of literature has consistently shown schizophrenia patients to be significantly impaired on tasks assessing emotion perception for faces (e.g. whether the face depicts sadness, happiness, surprise, fear or anger) when compared to either healthy controls [112, 113], or patients diagnosed with bipolar affective disorder or depression [114–118]. These impairments in facial emotion perception have been likened to that observed in right-brain-damaged patients [119, 120]. Perception of vocal affect has also been extensively investigated, and impairments in this social cognitive ability are well-established in schizophrenia patients [121]. Similarly, there is good empirical evidence that ToM deficits are particularly characteristic of schizophrenia [122, 123], although impairments have also been seen in bipolar affective disorder [124]. Maladaptive attributional styles, namely a tendency to attribute bad events to others and good events to oneself and the tendency to jump-to-conclusions, have been consistently observed in paranoid/psychotic

patients when compared to healthy controls or depressed patients [125–131]. Social perception, although less-extensively examined, has also been shown to be impaired in schizophrenia patients, demonstrated by measures of social cue recognition, which require the ability to decode non-verbal communications [132, 133]. Lastly, social knowledge, assessed using the Schema Component Sequencing Task, has also been found impaired in schizophrenia patients compared to non-clinical controls [134]. In summary, pervasive impairments in numerous areas of social cognition are commonly found in patients with schizophrenia and schizophrenia-spectrum disorders.

These social cognitive deficits are also apparent early in the course of psychotic illness and have been shown to be as severe as those observed in chronic schizophrenia [135, 136]. A number of studies in FEP have found significant impairment in emotion perception including facial affect and affective prosody recognition [113, 135, 136]. Further, performance on ToM and global social intelligence tasks (which involved ToM, attributing intentions to others, emotion perception, and the ability to interpret social context), are significantly impaired in FEP patients compared to controls [137]. These findings suggest social cognitive deficits are trait-like characteristics of the illness, where complex social cognitive skills are not adequately developed during the critical period of maturation. It may be that social cognitive deficits are vulnerability markers for schizophrenia, given that impairments in facial affect recognition [138], ToM [139] social perception [136, 140] and attributional bias [141] have also been observed in patients at ultra-high-risk (UHR) of developing psychosis. To further support this hypothesis, deficits in emotion recognition [142–144], ToM [145–150] and social perception [146] have also been observed in first-degree relatives of schizophrenia patients.

Genesis: Getting at the Root of Social Cognitive Deficits

The findings described above are in line with the neurodevelopmental hypothesis of schizophrenia. Although basic cognitive and brain functions are for the most part in place by school age, significant maturation continues throughout and after puberty. For individuals who develop a psychotic disorder like schizophrenia, the FEP is typically around age 20, yet "pre-psychotic" symptoms often emerge earlier during adolescence [151], a time of increased vulnerability to many psychiatric disorders [152]. The exact reason for this is unknown, but may be related to abnormal maturation of the brain during adolescence. It is now known that the adolescent brain undergoes substantial changes in white and grey-matter volume as part of the normal neurodevelopmental process [153]. Longitudinal magnetic resonance imaging (MRI) research has shown that individuals with childhood-onset schizophrenia have a significantly greater loss of frontal, parietal and temporal grey matter during mid-adolescence compared to healthy controls [154, 155], implying that abnormalities in the maturation of these brain regions may be implicated in the pathogenesis of psychotic disorders. Adolescence is also a time of psychological change, where an

individual becomes more interested in peer and social interactions, more self-aware, and starts to develop self-concepts and a personal identity [152, 156]. This shift in social behaviour and thinking may partly result from the maturation of the "social brain", in particular the medial prefrontal cortex (mPFC), superior temporal sulcus (STS) and anterior cingulate cortex (ACC) [157]. Thus, abnormalities in the maturation of brain regions involved in social thought/processing during adolescence may be the cause of social cognitive deficits in psychosis. While there is evidence linking structural abnormalities of the mPFC and ACC to deficits in emotion perception in chronic schizophrenia [158, 159], the link between social cognitive development, adolescent brain changes, and subsequent risk factors for developing a psychotic illness, has yet to be fully characterised.

The Impact of Social Cognition on Functioning

It would appear nonsensical to deny that a strong influential relationship exists between social thinking and social behaviour in schizophrenia. Nonetheless, there is limited research that has directly investigated the impact of social cognitive abilities on functioning. The focus, until recently has been predominantly directed towards non-social cognition, often referred to as "neurocognition" for distinguishing purposes. A number of research studies have shown social cognition to be a better predictor of social functioning than neurocognition [134, 160–162]. There is some debate as to the degree of overlap between neurocognitive and social cognitive thought processes, although neuroimaging findings to date provide evidence for distinct neural underpinnings of social cognitive abilities that are partially independent of non-social neural processes, including executive functions and sequence learning [163]. Recent research suggests social cognition may be a mediator between neurocognition and social functioning [164–166]. Despite the evident and logical relationship between social and non-social cognition, research supports the two as independent constructs that contribute unique variance to the prediction of social functioning and interpersonal skills [134, 167]. Specifically, research in schizophrenia patients has found emotion perception to be linked to social competence, independent living, community involvement and interpersonal relationships [168, 169]. Similarly, social perception has been strongly linked to social behaviour [170, 171] and vocation-related social skills [161]. Indirect measures of social perception, such as the visual perception of biological motion (i.e., the movement of the body or limbs), have also been found to impact significantly on role functioning [166, 172]. Studies have shown poor ToM to explain 24% of the variance in social behavioural abnormalities [160], and to be associated with poor social functioning and interpersonal skills in both the early and late stages of schizophrenia-spectrum disorders [134, 173]. There is limited research into the effects of attributional style on social functioning, however "hostile" attributional bias has been shown to predict aggressive behaviour [174], while "stable" attributions have been linked to good community functioning [175]. Interestingly, Penn et al. [162] found that poor

performance on information processing of social rather than non-social information was more strongly related to maladaptive ward behaviour in patients with schizophrenia.

Interventions Targeting Social Cognition and Social Functioning in Psychosis

Given the above findings, the National Institute of Mental Health (NIMH) – Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative identified social cognition as one of the key targets for development of new treatment interventions in schizophrenia and other psychoses [176]. However, the concept of treating such deficits is not new, with numerous researchers beginning the development of training tools as early as 1995 [177]. Since then various therapies have been evaluated using randomised controlled trials.

Neurocognitive Enhancement Therapies with an Adjunctive Social Component

One of the first research groups to incorporate a social cognitive element into their therapy program combined it not only with cognitive remediation but also with work therapy (WT) [178]. Neurocognitive enhancement therapy (NET) involved cognitive computer-based training for up to 5 h/week for 26 weeks, plus weekly group meetings where each week one participant would prepare and present an oral presentation. This was based on an exercise used in Ben-Yishay et al.'s [179] traumatic brain injury program, and was intended to engage social information processing skills. Significant improvements in performance were observed on the Bell-Lysaker Emotion Recognition Task at the end of the 6-month program. Participants who received NET plus WT worked significantly more hours than the WT only group at the 12-month time-point [180]. Authors extended this research by increasing NET to 1 year and adapting the WT component to focus on competitive employment opportunities rather than work placement (which was within the medical centre from which participants were recruited). While there were no significant effects on performance of social cognitive tasks after 1 year of therapy [181] there was a beneficial effect on the cumulative rate of competitive employment at the 2-year time-point [182].

Cognitive Enhancement Therapy (CET) [183, 184], although largely designed to improve fundamental neurocognitive processes, devotes a proportion of training to improving global social cognitive functioning, and also adopts concepts from Ben-Yishay et al.'s [179] program. Cognitive Enhancement Therapy is highly demanding and involved, where participants attend twice-weekly training sessions for 2 years, and active involvement of the treating clinicians/teams in the formal evaluation of their clients' cognitive styles and a corresponding coaching plan is expected. The

first 6 months consist predominantly of computer-based work with a partner and is aimed at improving attention, memory and problem solving. The second phase includes the continuation of weekly computer training once a week plus weekly group meetings involving exercises designed to enhance context appraisal, perspective taking, gist acquisition and automatic/parallel processing of social information [183, 184]. CET has been shown to improve social cognition at the completion of 2-years training and at 1-year post-training in chronic schizophrenia and schizoaffective outpatients [185, 186]. It is important to note, the authors defined social cognition as "awareness of relationship aspects" and assessed this domain with a 50-item checklist based on patient and observer report on various behaviours relating to four factors (tolerance, support, perception and self-confidence). Given this non-conventional measure of social cognition, findings are difficult to interpret and may be more indicative of personality traits. Preliminary analysis of data from a similar study in less chronic patients (illness duration <8 years) showed 1 year of CET in comparison to 1 year of Enriched Supportive Therapy (EST) significantly improved performance on an emotional intelligence (EQ) test [187]. A 2-year follow-up study later found social cognition (based on the same EQ measure and clinician-rated assessments) as well as social functioning (based on behavioural measures addressing for example: peer relationships, interpersonal anguish, social leisure, activities of daily living and global functioning) to be significantly enhanced with CET [188]. In addition, after 2 years, 54% of participants who received CET were actively engaged in paid, competitive employment, which was significantly greater than those from the EST group (18%). Extension of this research has recently implicated CET as a neuroprotective mechanism against grey-matter loss in the left hippocampus, parahippocampal gyrus, and fusiform gyrus of schizophrenia patients [189]. Participation in CET compared to EST was also associated with enlargements in left amygdala volume. Interestingly, performance on social cognitive measures was mediated by the effects of CET on grey matter preservation in the left parphippocampal gyrus, fusiform gyrus and amygdala [188], implying CET potentially facilitated neurogenesis and enhanced brain functioning in this region. However, this is highly speculative and findings of enlarged amygdala volumes in bipolar and affective psychoses patients receiving standard treatment [190, 191], further brings into question the underlying neurobiological mechanisms driving these brain changes. Further investigation using functional MRI techniques is warranted.

Targeted Training for Specific Social Cognitive Impairments

Highly specialised training approaches aimed at improving one area of social cognition, namely affect recognition, have been suggested for improving social functioning [192]. A pilot study of a brief (three 15 min sessions over 1 week) computerised emotion recognition program originally designed for autistic children, was able to enhance facial emotion recognition performance of chronic schizophrenia inpatients [193]. Wolwer et al. [194] investigated the 6-week (12-session) program

Training of Affect Recognition (TAR), in a large ($N = 77$) randomised controlled trial in non-acute schizophrenia patients. The training was computer-aided but also involved desk-work and was performed in groups of 2. The content focused on restitution and compensation strategies, direct positive reinforcement and feature abstraction, with an emphasis on the importance of verbalisation of the characteristic features of facial affect. TAR was shown to be superior to CRT and TAU for improving performance on a multiple choice facial affect recognition task. No measures or indices of functional outcome were administered.

Another program that has been used to specifically treat facial emotion recognition deficits in schizophrenia is Ekman's Micro-Expression Training Tool (METT; for the latest version see http://www.paulekman.com/). The METT is a computer-based program, which involves videos with verbal explanations, training tasks with feedback on performance, and post-training review videos. Training takes approximately 40–60 min to complete. Russell et al. [195] found that chronic schizophrenia patients improved significantly in emotion recognition of faces that were familiar (used during training) as well as novel faces (from Pictures of Facial Affect [POFA library] [196]) immediately after training, which was sustained after 1 month post-training. When only subtle emotions were used from the POFA library, improvements were observed at 1 month post-training in the subset of patients ($N = 10$) who were followed up, but no improvements were observed immediately after training. This suggests a possible learning effect over the 1 month with repeated exposure to real-world situations and an increasing awareness of the facial emotions expressed by others. Worth noting is that a lower baseline Social Functioning Scale score was a significant predictor of poorer performance on this latter task, further suggesting exposure to real-life social situations may be important for maximising training effects. However, baseline working memory and general face processing abilities were also significant predictors of post-training performance on this task, further highlighting the intricate relationship between social cognition, neurocognition and social functioning.

Although TAR and METT were successful in treating facial emotion recognition deficits, impairments in schizophrenia are not restricted to just one construct of social cognition. Thus, broader all-encompassing approaches have been suggested to be more beneficial and practical, with a greater likelihood of enhancing functional outcome.

Training Programs with a Focus on Social Cognition

Social Cognition Enhancement Training (SCET), which utilizes cartoons as an aid for training exercises, has been developed and tested in schizophrenia patients in community-based rehabilitation settings [197]. Choi and Kwon [197] found performance on the Korean version of the Picture Arrangement (PA) task [198], which was administered as a measure of social perception, to improve significantly over the 6 months of training in comparison to the control group. However, this finding is questionable given that practice effects were not accounted for and the same PA

task appears to have been administered at baseline, and at 2, 4 and 6 months. There were no differences between groups for the other two measures of social cognition (a schema sequencing task and a pictorial contextual/emotion recognition test) at the 6-month assessment. Furthermore, no indices of social functioning, general functioning or psychopathology were reported.

Metacognitive rehabilitation strategies have also been applied with the aim of enhancing ToM abilities through mediated learning and exposure to new experiences. Metacognition can be defined as "thinking about one's thinking, and involves the ability to monitor decision-making, information gathering, and to cope with basic cognitive limitations" [199]. Roncone et al. [200] devised a 22 week group program based on previously suggested treatment goals for individuals suffering from learning disorders [201]. Although the therapy was fundamentally neurocognitive-based, activities were non-computerised and embedded within social contexts. For example, the majority of training (16 sessions) was aimed at learning how to observe the emotions of others, how to communicate one's own feelings, how to make new friends (by developing intrinsic motivation), and to try and recognise the beliefs held by other people. Pilot data demonstrated significant improvements in performance of ToM tasks and a measure of global functioning at 6 months, in contrast to the control group who received antipsychotic medication and supportive psychotherapy alone [200]. To our knowledge, no further documented findings have been published. A similar intervention, the Metacognitive Skills Training (MCT) program, was developed and tested by Moritz et al. [199] who reflect on the theoretical models that implicate dysfunctional ToM and attributional biases as the primary cause of false beliefs and delusional thinking in psychosis [202–206]. The MCT program is designed to facilitate participants' awareness of cognitive difficulties, to encourage them to critically reflect on these, and to complement or change their current thinking styles accordingly. The MCT modules address the following issues: self-serving bias, jumping to conclusions behaviour, bias against disconfirmatory evidence, deficits in ToM, overconfidence in memory errors, and depressive cognitive patterns [199]. Following the pilot study [207], the authors conducted a randomised controlled trial with inpatients from a university hospital in Germany [208]. Preliminary data from a small sample ($N = 30$) suggested 4 weeks of MCT may be beneficial for reducing positive symptoms and jumping to conclusions bias. However, findings were not statistically significant, thus larger studies are required before any inferences can be made.

Social Cognition and Interaction Training (SCIT), developed by Penn et al. [209] is a manual-based 6-month group intervention program that also involves metacognitive training principles and addresses multiple aspects of social cognitive functioning. While it appears similar to SCET it is structured very differently and comprises three distinct phases: (1) emotion training which involves 6 sessions focusing on defining emotions, emotion mimicry and understanding paranoia, (2) figuring out situations which involves 7 sessions focusing on distinguishing facts from guesses, jumping to conclusions, understanding bad events, and (3) integration which involves 5 sessions dedicated to checking out guesses in real life by using patients' own examples of past social interactions as well as role play. Following

the successful pilot study [210], a randomised trial that compared SCIT to a coping skills control group (which focused on problem-solving, symptom management and relapse prevention), found SCIT to be significantly more effective at improving performance on measures of emotion perception, social perception, ToM, and attributional style [211]. Aggressive behaviour, patient's need for closure (related to patient's ability to cope with ambiguity and being open-minded) and social relationships (based on self-report) also improved with SCIT. Moreover, social functioning (based on the Social Functioning Scales: engagement and interpersonal [212]) improved significantly with SCIT training in comparison to the control group, and was independent of change in psychopathology. The main limitation of this study was that all participants were from a forensic psychiatric treatment facility and had a mean illness-duration of 18–19 years, thus limiting generalisability to less chronic samples. However, a more recent quasi-experimental study with schizophrenia outpatients ($N = 30$), found SCIT plus TAU in comparison to TAU alone, significantly improved performance on a facial emotion identification task and a role-play measure of social skill [213]. Roberts et al. [214] have recently tested the transportability and feasibility of SCIT with an open trial in a community sample. Again, significant improvements were observed on the same emotion perception task, with the addition of improved performance on the Hinting task [206], a measure of ToM ability. Evaluation of the program by clinicians and patients was positive overall, with patients generally rating the SCIT sessions as either "helpful" or "very helpful". The SCIT program has now been integrated into regular clinical practice within select mental health services throughout New York City [214].

In regards to research assessing the effects of both SCET and SCIT, follow-up assessments were conducted soon after training had been completed (ranging from immediately after completion to 6 months post-intervention). It is unknown whether the skills acquired and enhanced level of social cognition persisted in the long-term after training had ceased.

Interventions Targeting Vocational Outcome

Being unemployed, even in the absence of mental illness, limits the degree to which one can participate in society or the economy, increases the risk of alcohol or other substance use, is a risk factor for the onset of mental illness, and can place pressure on current relationships or make starting new ones difficult. It also means the unemployed individual is unlikely to access the benefits of living in society, obtain quality housing, or build a future through savings. For those with mental illness, unemployment reinforces social and economic marginalisation, has the potential to exacerbate symptoms, increases risk of homelessness, and often persists after other symptoms of illness have resolved.

A number of RCTs have now been conducted with Individual Placement and Support (IPS) in populations of people with chronic illness. This form of supported employment differs from previous treatment models in that it focuses on rapid job

search and placement as well as support following the acquisition of a competitive position [215]. An earlier Cochrane review found that there was a 18–41% difference in favour of supported employment [216]. A more recent review of 10 RCTs of IPS in populations with chronic illness has found a difference of 23–60% in terms of competitive employment [217]. Further, the IPS groups in these studies produced shorter times to commencement of employment, and longer duration of employment than control conditions [217].

Evidence suggests that for young people in particular, periods of unemployment can have "scarring" effects on future employment opportunities increasing the risk of longer term poverty and social exclusion [218]. There have also now been three RCTs of supported employment in FEP [219–221], including one (the first) conducted by our group. This allowed us to identify and overcome challenges associated with establishing this intervention [222]. Despite being significantly lower on functioning at baseline, the IPS group gained significantly more jobs in total (23 vs. 4), earned significantly more money (median $2432 vs. $0), and worked longer (median 5.0 vs. 0.0 weeks) than those who did not receive IPS. The percentage of those dependent on benefits decreased significantly in the IPS group, while there was no change in the control group. Two other RCTs have recently replicated our results demonstrating that IPS is effective at helping young people with FEP obtain employment [219, 220]. As a point of comparison, 10 control group participants in our study accessed government-funded employment agencies, but none obtained employment. One had a single interview. While the outcomes in terms of obtaining employment are good, the duration of employment is an area that needs improvement.

Conclusions and Future Directions

Functional Outcome Measures: Past Issues and Future Challenges

The continuing disability of patients, often despite remission of psychotic symptoms, has prompted not only new treatment strategies but also discussions surrounding the concept, definition and measurement of functioning. In 2005 the NIMH convened a workgroup to assess the issues relating to functional outcome measures and their suitability for use in clinical trials [223]. Among the various issues discussed were the advantages and disadvantages of different forms of assessment strategies (i.e. clinician rated, blind professional rated, self-report, informant report, behavioural observation), all of which were deemed utilisable depending on the research question being explored. For example, self-report measures can be very informative, particularly when assessing constructs such as quality of life or perceived satisfaction with current role functioning. However this method may be less reliable in severely ill patients who lack insight and have difficulty making objective self-appraisals. Suitability of a particular measure will thus depend on the setting in which patients are in (i.e. hospitalised vs outpatient, homeless vs government/family

supported housing) and their state and stage of illness (acute vs stable, FEP vs multiple episodes vs chronic). The workgroup also acknowledged that the validity of a functional outcome measure will in addition rely on inferences about performance demands, the skills, knowledge, and abilities of individuals, theories of dysfunction and the relationships between all these factors [223].

To date, the definition of "community functioning" continues to be open to interpretation, with researchers and clinicians typically defining it as overt behaviours (such as activities of daily living, living independently) and role function (i.e. work, friends, spouse, family), while consumers tend to conceptualise functioning and recovery in terms of feelings of hope, empowerment and fulfilment [224]. The lack of a consensus on what is considered "normal" functioning also poses a challenge for the development of new reliable measures, which is largely dependent on cultural context.

Recently, the U.S. Food and Drug Administration introduced the regulation that all treatment trials aimed at enhancing cognition in schizophrenia also include a co-primary outcome measure of functional capacity [225]. The purpose of having a more ecologically valid tool was in order to portray meaningful endpoints to consumers and clinicians. To that end the MATRICS Outcomes Committee assessed the reliability, validity and appropriateness of four potential measures of functioning, two of which were interview-based measures of cognition (the Schizophrenia Cognition Rating Scale [226] and the Clinical Global Impression of Cognition in Schizophrenia [CGI-CogS] [227]) and two were role-play functional capacity measures (the Maryland Assessment of Social Competence [228] and the UPSA) [229]. All four measures were found to be psychometrically sound, although the "medication management" component of the UPSA had poor test-retest reliability. Practice effects over time were generally small (Cohen's *d* ranged from 0.04 to 0.23), yet all measures but the CGI-CogS had at least one subscale/component that produced ceiling effects. Functional capacity measures tended to be more strongly correlated with an overall cognitive performance composite score than the interview-based cognitive functioning measures. Surprisingly, all measures were at best, only modestly correlated with self-reported functional outcome, including social, independent living and work/school functioning. In addition, preliminary data presented at the 2nd Biennial Schizophrenia International Research Society Conference 2010 suggested that U.S. developed measures, such as the UPSA, may not be appropriate for use in less developed countries, namely China [230]. Notably, acculturation, literacy, education and cognitive abilities, all increase the difficulty of creating reliable cross-cultural intermediate measures of functioning in the future.

In addition to selecting a reliable and valid functional outcome measure, it is important to use an adequate control condition or comparison group, in order to assess the true potential of any given intervention or treatment regime. This is particularly important for therapy aimed at social and/or neurocognitive enhancement, as the simple act of socialising with a group of peers or focusing on a computer task may have positive non-specific effects that may or may not be to the magnitude of that produced by the active intervention. New analytical strategies have also been suggested as a means of testing theoretical models of functioning, such as structural

equation modelling and path analysis, with the aim of exposing underlying factors and potential mediators and moderators for predicting functional outcome [223]. As mentioned earlier, one proposed mediator between neurocognition and functional outcome is social cognition, an area that continues to receive increasing attention and is considered prominent in certain theoretical models of functional outcome in schizophrenia [231]. Lastly, longitudinal studies are needed to assess real-world functional achievements and to determine whether short-term interventions have enduring effects.

New Approaches to Intervention Programs

In the same way that clinicians treat psychotic symptoms, with multiple treatment approaches such as medication, CBT, and family therapy, so too should be the case for treatment of functional impairment. Therefore, future research should attempt to adopt a combination approach. This multimodal treatment model has substantial support [46, 178, 180, 183]. As mentioned earlier, NET combined with WT was successful at improving performance on both neurocognitive measures and vocational outcome [178, 180]. However, the social component was social-skills based and therefore did not explicitly address specific social cognitive deficits, which may provide more sustained effects on functional indices. At present, it is unknown as to whether these programs have any influence on functional milestones other than vocation, such as peer relationships, independent living and community activities. Research into the effects of combined SCIT and the vocational intervention IPS is currently underway in a FEP population by our research team at Orygen Youth Health Research Centre.

In terms of intervention strategies, future research is set to focus more efforts on metacognitive approaches [199, 200, 232, 233], which encourages participants to monitor and voluntarily take control over their cognitive abilities, thinking styles and actual performance. This is expected to produce more meaningful sustained effects on real-world functional outcome. Horan et al. [234] further suggest patients' "attitudes" towards functioning also need to be addressed, where the common "defeatist-realist" attitude can often confound self-report assessments and block any potential of learning from intervention programs.

Pharmacological interventions have also been suggested to enhance functional outcome indirectly via improved neurocognition and social cognition. A number of research groups have investigated the effects of antipsychotic medication on social cognitive performance specifically. A recent review of eight studies concluded that neither typical nor atypical antipsychotics had a significant impact on facial affect recognition where patients had been re-assessed between 2 and 8 weeks following treatment [235]. Despite this, findings from the Clinical Antipsychotic Trials of Intervention Effectiveness study have shown facial emotion perception (specifically discrimination) to improve significantly following 2 months of perphenazine treatment [236]. However, none of the other antipsychotics that patients had been

randomised to (including risperidone, quetiapine, olanzapine and ziprasidone) had any significant effects on performance over time, nor were there any differences between treatment groups. Evidence of positive antipsychotic effects on ToM have also been observed with 2 and 6 weeks of antipsychotic treatment, although this was a non-randomised design and patients were on varying types of medication [237]. Conversely, Sergi et al. [238] found no effect of risperidone, olanzapine or haloperidol on multiple measures of social cognition in an 8-week randomised double-blind study. Despite early drug research in this field and the few significant results reported here, antipsychotic treatment is now widely acknowledged as having minimal if any significant effects on cognitive performance in schizophrenia and psychosis [239].

More promising findings come from research of less conventional pharmacological agents, namely oxytocin. Research into the effects of nasal delivered oxytocin treatment on social cognitive performance in schizophrenia is currently underway at the Brain and Mind Research Institute at the University of Sydney. This research is driven by significant positive effects of intranasal oxytocin treatment on mental representations of the self (i.e. ToM) in individuals diagnosed with social anxiety disorder [240]. Moreover, a double-blind placebo controlled cross-over design found a single dose of oxytocin nasal spray significantly improved emotion perception for adolescents (aged 12–19 years) with either Asperger's Disorder or Autism [241].

Other forms of innovative treatment currently being explored include recombinant human erythropoietin, which has been found to enhance cognitive performance (but not social functioning) when administered for 3 months as an adjunct to antipsychotic medication in chronic schizophrenia patients [242]. Similarly, herbal and natural medicines are also in the early phase of testing but have produced some promising results. Warm-supplementing kidney yang, a Chinese herbal medicine, added to risperidone for 8 weeks has been found to significantly improve social functioning (assessed with the social disability screening schedule) in comparison to a placebo [243]. Omega-3 polyunsaturated fatty acids also show potential for beneficial effects on functional outcome, as evidence shows 3–4 months of adjunctive eicosapentaenoic acid treatment to have beneficial effects on psychopathology [244, 245]. Furthermore, a randomised, double-blind placebo-controlled trial of 12 weeks omega-3 in an UHR sample revealed a partial protective effect in terms of transition to psychosis [246]. This fish oil treatment was also effective in reducing symptomatology and improving overall functioning (measured using the GAF), suggesting a natural alternative to the somewhat controversial use of antipsychotic treatment in this early phase of illness.

The Way Forward Lies at the Beginning

The majority of targeted social and vocational interventions have been trialed in groups with established illness, where for a variety of reasons, it may be argued there is less potential gain. The advantage of applying interventions aimed at a group of

young people with FEP or at UHR of psychosis are that higher-order cognitive and social cognitive processes are still developing [247, 248], and those individuals are not as removed from their original functional trajectories. That is, even if the deficits are as significant early in the course of the first episode of illness in comparison to later stages, there is greater scope for significant functional improvement and the prevention of functional decline [249] due to the greater brain plasticity associated with ongoing neurodevelopment in this phase of life [157].

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Chapter 10
Revisiting Cognitive Remediation for Schizophrenia: Facing the Challenges of the Future

Caroline Cellard, Sasha Whaley, and Til Wykes

Abstract It is now well established that cognitive impairments are evident in people with a diagnosis of schizophrenia as well as in their unaffected relatives. However, improving cognition is a relatively new interest in schizophrenia research which has developed over the past 15 years with new treatments and rigorous studies of efficacy. This relatively large body of work suggests that cognition can be improved significantly by cognitive remediation therapy and that these changes can impact on everyday functioning including work outcomes. There are a number of challenges for the future; not only to be clearer about the measurement of the success of programmes, but also to improve the delivery of this promising psychological treatment. Identifying mediator and moderator variables may help in the understanding of the active ingredients of therapy as well as the course of the clinical disorder.

Keywords Schizophrenia · Cognitive · Training · Rehabilitation · Methodological

Abbreviations

CNTRICS	Cognitive neurosciences treatment research to improve cognition in schizophrenia
CREW	Cognitive remediation experts workshop
CRT	Cognitive remediation therapy
MATRICS	Measurement and treatment research to improve cognition in schizophrenia
NICE	National Institute for Health and Clinical Excellence
PORT	Schizophrenia patient outcomes research team

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Cognitive deficits are key features of schizophrenia. They are observed in areas such as attention, memory and executive function (e.g. [1]), and can act as a "rate-limiting factor" for other psychological or rehabilitation interventions [2, 3]. Targeting cognitive deficits as a treatment outcome is of particular relevance because they are associated with social functioning in schizophrenia [4, 5]. Furthermore, existing treatments such as first and second generation antipsychotic medications are mainly effective on symptoms and have small effects on cognition [6, 7].

The understanding of the role of cognition in schizophrenia and its treatment has been boosted by the creation of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) neuropsychological battery which allows comparisons across studies [8], and more recently by the Cognitive Neurosciences Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative [9] which will enable more in depth measurements to be carried out. The development of a psychological treatment, cognitive remediation in its different forms has also allowed us some insights into the role that cognition plays in the recovery of people with schizophrenia. But we are not yet at a point when health care systems have accepted that these treatments should be offered within any healthcare package for people with schizophrenia. The "tipping point" we think is near at hand and this chapter will explain why this may be important for research, for treatment options and for our consumers.

Cognition as a Key Factor in Schizophrenia

Studies aimed at identifying cognitive deficits in schizophrenia have rapidly expanded in the last two decades. A search on PubMed with keywords "schizophrenia" and "cognition" showed an increase of papers ranging from 47 in 1989 to 694 in 2009 (see Fig. 10.1) (see also [10]). This clearly illustrates the

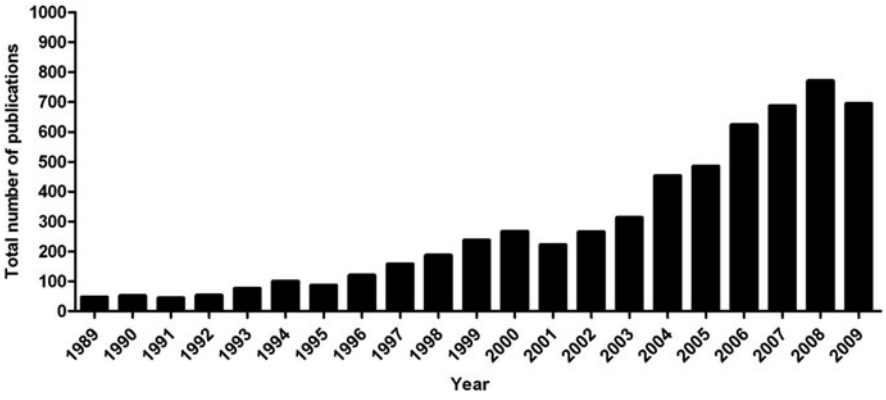

Fig. 10.1 Total number of publications each year over the last two decades (keywords: "Schizophrenia" and "Cognition")

growing interest in cognitive dysfunction in people with schizophrenia. Meta-analyses comparing the cognitive performance of patients with schizophrenia to a healthy control population suggest major effects on key cognitive domains with the largest effect sizes in memory and processing speed [1, 11, 12]. Although measured on neuropsychological tests, these cognitive functions are clearly essential to functioning efficiently in the real world.

Cognitive deficits in schizophrenia are pervasive throughout the course of the disorder. They have been observed not only in populations at high risk of the disorder because of close family ties to a person with a diagnosis of schizophrenia (e.g. [13]), but they are also found in patients experiencing their first episode psychosis (e.g. [14]), in the immediate period before onset (prodromal stages) and even in early childhood (e.g. [15]). They are also observed to a lesser degree in unaffected relatives of patients with schizophrenia [14, 16].

The relationship between cognitive deficits, clinical symptoms and functional outcome is well supported. Difficulties with memory are associated with negative symptoms although mixed results have been reported for positive symptoms. Green et al. [5] observed that cognitive deficits can predict outcome in patients with schizophrenia. Clearly this begs the hypothesis that psychological treatments targeting cognitive deficits will impact on and benefit functioning although the mechanism for this impact has never been clearly described. However, we have known for some time that people with a diagnosis of schizophrenia and who have a cognitive deficit do not benefit as much from rehabilitation programmes [17]. Clearly if people with schizophrenia have concentration and memory difficulties then they will not be able to absorb. Treating cognitive deficits may also be considered as potential tools to protect or delay the onset of schizophrenia in a primary (e.g., ultra high risk population) and secondary (individuals with disease) prevention framework.

Cognitive deficits may also contribute to the understanding of the mechanism of the disease. For instance the Consortium on the Genetics of Schizophrenia report that both individuals with schizophrenia and their unaffected family members experience cognitive deficits. This suggests that rather than an outcome of the disease process, these deficits are part of the innate underlying distinct differences that make some individuals vulnerable to schizophrenia. In other words they may act as endophenotypes which are intermediate phenotypes hypothesised to be more proximal functions of gene action than the clinical manifestation of the disease itself [18, 19]. Candidate endophenotypes have been identified in attention, working memory and long term memory [18]. The hope of these studies is that this candidate endophenotype may enable not only the mechanism of gene effects to be identified but that resilience factors too may be recognized.

Finally, and most importantly, service users themselves report that psychotic symptoms are reduced with medication but that cognitive deficits are still present. These interfere with their everyday lives, reduce their confidence in their own self efficacy and hinder their recovery.

In summary, there is evidence of the pervasive presence of cognitive deficits that are noticeable to service users, their families and clinicians and have been identified as possible treatment targets as well as of scientific relevance in the understanding

of the disorder called schizophrenia. Recent publications have also debated whether there should be changes made to the criteria for schizophrenia so that they recognise the importance of cognitive deficits [20].

Efficacy of Cognitive Remediation Therapy in Schizophrenia

The scientific community clearly recognises the relevance of treating cognition in schizophrenia. Recent efforts to identify specific pharmacological treatments have not yet been successful but there have been developments of psychological treatments such as cognitive remediation techniques that seem to have identified reasonable effects. These treatments are not only important for easing the burden of cognitive dysfunction but they are also vital in our investigation of the causal models and pathways between cognition and outcome. These models will have relevance in our understanding of schizophrenia but may also lead to a wider understanding of neuroplasticity, cognitive capital and the effects of specific treatments to maintain cognitive capacity that may have wider implications for our understanding of human health.

A recent effort in the USA, the Working Group Conference on Multisite Trial Design for Cognitive Remediation in Schizophrenia, aims to design a multisite trial of cognitive remediation [21] in order to identify the effect of remediation across different service treatment centres. But evaluations of the benefits of cognitive treatments for schizophrenia have not been hampered by the inability to carry out multisite studies, rather they have been challenged by the lack of a clear definition of the treatment itself.

This gap was filled recently by the Cognitive Remediation Experts' Workshop in 2006 and ratified in 2010 where the agreed definition of cognitive remediation was as follows:

> Cognitive remediation for schizophrenia is "a behavioural training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition[1] or metacognition) with the goal of durability and generalisation" (Cognitive Remediation Experts Workshop (CREW), April, 2010).

Cognitive remediation has been found to be effective in a number of reviews and meta-analyses [22–26]. A recent meta-analysis by McGurk et al. [25] comprises 26 randomised controlled trials for a total of 1151 patients randomised to either a cognitive remediation program, treatment as usual or a treatment controlling for non-specific effects. This meta-analysis reports significant improvements on cognition ($d = 0.41$), symptoms ($d = 0.28$) and functioning ($d = 0.36$). The benefits are greater when cognitive remediation is delivered in a broader rehabilitation program. There are different programmes of cognitive rehabilitation, but so far there

[1] Social cognition, according to discussions at the NIMH meeting is defined as "the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviours of others".

is no indication that one program is better than another. The programmes differ in the way they deliver training and the specific aim of training such as whether they use only "drill and practice" or aim to improve strategic processing through "drill and practice plus strategy coaching". The programmes using the drill and practice plus strategy coaching ($d = 0.62$) showed greater generalisation in terms of their effects on functioning compared to drill and practice alone ($d = 0.24$) [25]. The effect of cognitive remediation therapy was also stronger where cognitive remediation was provided in the context of psychiatric rehabilitation ($d = 0.47$) compared to when it was provided alone ($d = 0.05$). The adjunctive rehabilitation programmes most often included work rehabilitation programmes, mostly supportive employment programmes. These programmes had typically shown that the group that receives both cognitive remediation as well as work rehabilitation opportunities increased the chances of getting and keeping a job, earned more money and generally worked more hours than those who received work rehabilitation alone [27, 28].

One example of a drill and practice plus strategy coaching therapy is Cognitive Remediation Therapy (CRT) [29] which aims to improve cognitive skills in people with schizophrenia. It focuses on cognitive flexibility, memory and executive function. This is a theory-based model driven therapy that is characterized by a top-down approach. The therapy is usually delivered in 40 sessions which take place at least 3 times a week and is delivered using pen and paper tasks with a therapist. Although this form of delivery is considered a strength because it allows complete tailoring of the therapy to the patient's needs, it also produces a high level of therapist burden. Reducing this burden, perhaps through computerisation is of particular interest because it is characterised by ease of delivery as well as the ability to present materials within engaging media [30].

Computerized Cognitive Rehabilitation Programmes

General guidelines for computer-assisted rehabilitation and cognitive remediation have been suggested by Task Force report division 40 in 1991. One resolution states: "Appropriate clinical use of computer software in rehabilitation is dependent upon maintaining a clear distinction between software being properly viewed as a component in an organized treatment program versus being improperly viewed as treatment itself" [31, p. 5]. The guidelines suggest that a therapist can use computerised-assisted rehabilitation as a tool to provide challenges and engage their clients with multimedia. The therapist acts as a coach by teaching patients strategies to equip them with different ways to efficiently tackle the tasks. The therapist can then help the patient to transfer strategies they found useful to daily life encounters. For some patients using a computer can be challenging in itself. Using a computer skills questionnaire can aid in monitoring this.

A recent meta-analysis evaluated the efficacy of computerised-assisted cognitive remediation [32]. The meta-analysis comprises 16 randomised controlled trials comparing a computerised-assisted cognitive remediation group to a control group.

Computerised-assisted cognitive remediation was found to increase cognitive functioning with a medium effect ($d = 0.38$) on global cognition and had significant effects on attention/vigilance, working memory, verbal memory, processing speed and social cognition. Moderating factors such as age, treatment duration, weekly frequency and control condition type were also investigated but were not found to correlate with the effect sizes. Interestingly, the treatment effect was not found to be higher on targeted cognitive domains compared to non targeted ones. This suggests that computerised-assisted cognitive remediation has "non-specific" effects and targeting attention, for example, may not necessarily improve attention but may enhance other cognitive functions [32]. However, this result should be interpreted with caution because of the lack of statistical power and the small number of studies [32].

How Do We Measure Effectiveness in Cognitive Remediation?

This may seem a simple task-after all, cognitive remediation should do what it says on the tin – improve cognition. Cognitive performance has been the primary target of cognitive remediation in schizophrenia [21]. But cognitive dysfunctions are associated with poorer functional outcome [3, 33] which may be mediated by negative symptoms (see [34] for a meta-analysis). If functioning is the key outcome then some have argued that it must be the measure of a successful cognitive remediation programme.

The counter argument is that a change in cognition is usually associated with a change in functioning, but a change in functioning may not be associated with a change in cognition. So if cognition is the primary outcome in cognitive remediation therapy and therapy does not have a significant effect on cognition, do we continue to consider the therapy as efficacious? This issue arose in a study by Silverstein and colleagues [35] in which their intervention (shaping attention) had a clear effect on attention measured behaviourally at the end of therapy and this measure was related to the final outcome of a community rehabilitation programme. However, there was no evidence of improvements on the intermediate cognitive measures of attention.

Studies have shown that different cognitive remediation programmes produce varying effects on cognition and functioning. For example, "Drill and practice" type cognitive rehabilitation programmes produced the largest effect sizes in cognition. However, the programmes characterized by strategic learning produced the largest effects on functioning [25]. In other words, the programmes that produce smaller cognitive effect sizes can have a greater effect on functioning [36].

The alternative functioning measures are also not without their difficulties. The first problem with identifying functioning as an outcome measure is that the treatment duration is probably too short to observe a clinical change. Also any changes over longer periods of time may be caused by other factors, particularly the opportunities that may be offered for practising skills [21, 37]. Because of the delay in finding successful outcomes it has been suggested that an intermediate

measure, functional capacity, is a good candidate to evaluate the efficacy of cognitive remediation. Specific tests such as the University of California San Diego Performance-based Skills Assessment have been suggested but there is a high correlation between these types of task and more ecologically valid cognitive tests and so it is not clear whether they will provide an advantage over cognitive measures themselves.

In summary, cognition should be the key proximal target to evaluate the efficacy of cognitive remediation, so if cognition is not improved then the treatment can not be said to be effective. This relies on the sensitivity of our measures as well as an understanding of the theoretical model that drives therapy. Cognition and functional outcome are statistically associated but as functional outcome may take longer to be improved then the time frame for cognitive and functional improvements must be different. Functional capacity measures may fill the gap but it is not at all clear whether they offer any more benefits than ecologically valid neuropsychological tests. In addition any functional improvements may require additional rehabilitation efforts. This is unsurprising as it is probably a first step to generalise the skills from the specific therapy to the behaviour in the cognitive test situation. The second step is to generalise these skills to the everyday functioning. For example, after a broken bone heals physiotherapy is needed to improve the use of the limb, similarly cognitive remediation will improve cognition but the use of these skills in everyday life may need further therapy.

Critical Analysis of Neuropsychological Measures

Improvements in cognition can be assessed by a wide variety of measures whose methods differ substantially, including self report, specific and global interview measures as well as neuropsychological tests. Several cognitive parameters are gathered in a neuropsychological evaluation: accuracy of answers, number of errors made and time to do a task. Improvement is not always an increase in score, since reduction of errors committed is sometimes the targeted behaviour (e.g., reduction of perseverative errors in a Card Sort test).

What we are aiming to change in patients in cognitive remediation therapy needs further consideration. Specific outcomes may differ depending on the emphasis of the therapeutic programme. Some options are: to avoid errors, take their time in order to plan a task and to execute the plan correctly. As neuropsychological tests rely on changes in a total score and these scores are often made up of speed, errors or both then confusing results may be produced in a study. So if one compares control group participants (without the therapy) with the participants in the experimental group (receiving therapy) on measures of speed of processing then we may not find significant differences between groups because the patients receiving the therapy will have been taught to slow down in order to avoid errors. The experimental group may improve on other neuropsychological measures where the avoidance of errors drives the key test outcome. Selection of the key outcomes to the type of therapy is therefore important and comparisons between measures that rely on

different behavioural or strategic approaches will reveal specific effects of programmes. The outcomes in current use are often used without such subtle investigations producing a confusing picture of the pattern of change from one study to another and ensuring that meta-analyses produce lower effect sizes that do not reflect the true changes following therapy.

Choosing the right measures from within a neuropsychological battery is not just important for the overall estimate of effectiveness, it is also vital for teasing out the relationships between change in cognition and change in other assessments such as symptoms and social functioning. Brébion et al. [38] proposed the existence of two so-called distinct verbal memory systems that are differently related to symptoms in people with chronic schizophrenia. The first system is termed *memory efficiency* and refers to the production of correct responses. Memory efficiency is associated with depressive and negative symptoms. The other memory system is the *production of memory errors* such as intrusions (recalling an item not presented), list error (recalling an item presented previously) and false recognition of a non-presented item. Positive relationships were found between intrusions errors and delusions as well as between lists errors and hallucinations. It is possible that more associations between the positive symptoms and cognition might have been observed if errors or bias were identified as dependant measures in cognitive remediation studies.

Identifying key measures that might predict outcome is also difficult in the case of social outcomes. One method is to look at cross sectional relationships and choose measures of cognition that correlate well. However this method relies on static relationships identified cross sectionally. What we need to identify are those cognitive measures that are related dynamically to social functioning change. A study by Reeder and colleagues [39] found that memory and other measures were highly correlated with social functioning both at baseline and at follow-up and that scores on a Card Sort test were not correlated. However, it was only change in the card sort measure following therapy that was related to change in social outcome. This clearly demonstrates that static relationships may not identify the appropriate targets for therapy.

Another consideration is whether we should be aiming to increase or decrease a score as some cognitive deficits could lead to enhanced performance on some tasks. For example an inability to identify the global picture (or the gist) will not interfere with identifying a local stimulus and therefore there will be a lower level of interference than in people who are able to identify the global stimulus [40]. This is the superiority approach suggested by Knight and Silverstein [41] to overcome the problems of sensitivity of some cognitive tests.

A further factor to consider in terms of evaluating efficacy of cognitive remediation programmes is how broad a measure to use. Most neuropsychological tests are driven by many different cognitive skills such as memory, attention, concentration, vigilance, cognitive flexibility etc. Improvements in these tasks are therefore brought about by any one of the component skills. The purpose of CNTRICS was to identify measures that are more specific in that they rely on fewer cognitive skills or to ensure the major impact on change in performance is from one specific skill

only. The use of tasks tailored to measure specific processes is highly attractive as it would allow specific ingredients of a therapy to be measured. However, it may lead to unintended consequences if they are included in a study to identify overall effectiveness of a package of remediation because individual therapy participants will show individual patterns of change. This might mean that some change on Specific Measure A and others on Specific Measure B but not enough to show a significant difference on either measure. However, if a more global measure had been chosen which encompassed the skills from both A and B then it is highly probable that an overall effect would have been found. As these measures are so new this contention needs empirical testing by including both precise and general cognitive measures in the same study (see [36]).

In addition to traditional neuropsychological measures of cognition we might also use subjective measures to evaluate the effectiveness of cognitive remediation. Medalia et al. [42] compared the self reported awareness of cognitive deficits to actual performance on neuropsychological tests and found that about a quarter of the participants with cognitive deficits were not aware of their deficiencies. There is an assumption that as in other psychological therapies, it is of particular relevance that the patients are aware of their difficulties [42] and it has been argued that insight might be a mediator factor explaining the efficacy of the intervention and a key factor in the adherence to treatment. This argument seems tenuous at most as the cognitive deficits themselves might lead to insight problems which then lead to non-adherence.

In summary, cognitive measures have been chosen to measure key aspects of cognition which are known to be deficient in many people with a diagnosis of schizophrenia. However, there are some unintended consequences in the choice of outcomes. These include the chance of missing improvements because of the specificity of the measures, a lack of investigation of different patterns of cognitive performance that might have illuminated relationships of cognition, functional and symptomatic outcomes and a lack of specificity of the key changes that would be expected from cognitive remediation programmes that might be reflected in cognitive outcomes.

How Big a Change in Cognition Do We Need?

Effect sizes help us to identify the magnitude of the change and these are calculated by comparing scores between the experimental and control group. The change observed is described as statistically significant if it is unlikely to have been produced by chance. But what is important to participants, their families and the healthcare system is not the statistical significance but the level of change that is clinically meaningful. If a patient is able to remember seven digits after cognitive remediation, he will easily be able to learn the phone number of his friend. This may require an increase in working memory span from six to seven digits which is only a one point difference whereas statistical significance would only have been achieved through on average a two or three point difference. This is not an area which has

received any reflection in the field of cognitive remediation despite it being one that is considered by all other fields of psychological treatment.

Challenges for the Future: What Works for Whom?

Cognitive remediation as a field of research shows a significant growth in recent years. Since the McGurk et al. [25] meta-analysis, numerous papers have been published and the corpus of studies shows the efficacy of cognitive remediation with one sparse but notable exception [43]. After concluding that cognitive remediation therapy works it is now necessary to ask ourselves whether we can believe in the results gathered over the last two decades. Recent meta-analyses have not considered the external or internal validity of the studies generating the cognitive remediation effects and recent consideration of whether cognitive remediation should be included in evidence based guidelines has alluded to the possibility that studies without good methodology are driving the large effect sizes.

Wykes et al. [44] recently tackled this question using the Clinical Trials Assessment Measure (CTAM [45]) to evaluate the methodological quality of cognitive remediation trials in schizophrenia. The main problems highlighted for internal validity were: small sample sizes, lack of independent randomisation, assessor masking of group allocation and treatment fidelity assessment. It was concluded that the benefits of therapy cannot be attributed to methodological inadequacy because of the absence of relationship between a global index of cognition and methodological items evaluated with the CTAM. In fact Wykes et al. [44] found the methodological quality of studies to be acceptable, suggesting that valid conclusions can be drawn from these studies (see Fig. 10.2).

Fig. 10.2 Drawing valid inferences from the evaluation of efficacy of cognitive remediation therapy programmes

What Is the Next Generation of Research?

Cognitive remediation therapy in schizophrenia may now be facing the era of "second-generation research" (see [46] for a similar approach). Researchers may want to know *why* it works, *when* it is efficient and for *whom* particularly [47]. These questions evaluate the mediator (why) and moderator (when, whom) mechanisms at play (see [48] for a discussion). Knowing more about the mechanisms will allow researchers to develop targeted treatment packages with the highest chance of achieving the participants' own therapeutic goals.

Why does it work? – identifying mediators
Mediator: The process, mechanism, or means through which a variable produces a particular outcome. Beyond knowing that A may cause B, the mechanism elaborates precisely what happens (psychologically, biologically) that explains how B results ([49], p. 117).

Therapy and patient characteristics are attractive variables to investigate in order to better understand why cognitive remediation therapy works (see Fig. 10.3, see [48] for a similar approach). Key characteristics that deserve more attention are: duration and frequency of sessions, duration of trial, degree of therapist involvement, format of therapy (individual versus group), computerised versus non-computerised methods.

Within-group factors may also be associated with better outcomes such as symptoms, self-esteem, motivation and attendance. These variables are particularly difficult to identify from meta-analysis as the study means tend to provide little variance to disaggregate even though the studies themselves might have had a varied sample of participants.

When and for whom does it work best?
Moderator: A variable that influences the relationship of two variables of interest. The relationship between the variables (A and B) changes or is different as a function of some other variables (sex, age, ethnicity). ([49], p. 117).

Identification of moderator variables will help researchers to better identify who may particularly benefit from cognitive remediation therapy and whether these variables enhance or reduce the potential to benefit. These include gender, onset (recent versus chronic), education and age (see Fig. 10.4, see [48] for a similar approach).

Gender is relevant because men and women with a diagnosis of schizophrenia exhibit differences in symptoms as well as in cognition [50]. For instance, Longenecker et al. [51] suggested that women have better cognitive functioning than males. Participant age has been investigated by Wykes et al. [52] and McGurk and Mueser [53] who both found that younger patients benefited more from a cognitive intervention compared to older patients. A randomised controlled trial conducted by Dickinson et al. [43] also showed no benefit of cognitive remediation in one of the oldest groups of participants.

Even though the field of cognitive remediation therapy is growing and is in the stages of "second-generation research" it is not yet recommended in evidence based

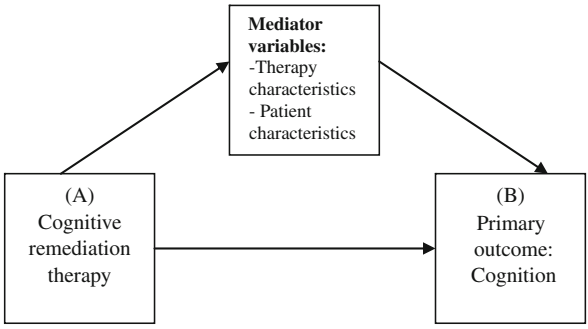

Fig. 10.3 Why: mediator variables to investigate in cognitive remediation therapy

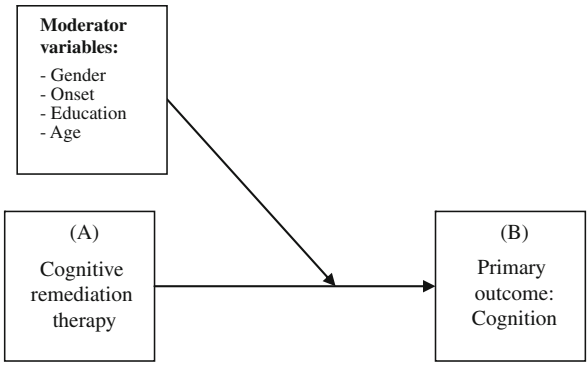

Fig. 10.4 When and whom: moderator variables to explore in cognitive remediation therapy

guidelines such as the US based Schizophrenia Patient Outcomes Research Team (PORT) and the UK National Institute for Health and Clinical Excellence (NICE). PORT carried out an evaluated cognitive remediation in 2009 and concluded that further work is needed [54]. They reported that variation among cognitive remediation programmes, particularly in their conceptual frameworks and also commented that rigorous clinical trials represent a minority of studies. These issues will hopefully be addressed by the multisite study due to take place in the USA and by more randomised trials in the next few years. NICE guidance was based on few studies as their inclusion criteria were very tight including not depending on post treatment cognitive outcomes and assuming that functional outcomes were paramount. Since their evaluation there has been several new trials added as well as clear analysis of the effects of the quality of the methods used.

Additional Considerations for Evaluations of Cognitive Remediation Therapies

The effects of cognitive remediation can also be measured by looking at cost-effectiveness analyses and in particular the effects of cognitive remediation on service utilisation. However, it is difficult to establish whether a good outcome from the intervention should lead to an increase or reduction in service use [47]. This is because effective cognitive remediation may lead to improved independence and less dependence on support by the psychiatric or social care agencies. Alternatively they may lead to increased attendance in social rehabilitation programmes which may over time improve the quality of life of the participant. A formal health economic analysis was provided for the randomised trial carried out by Wykes et al. [55] (see [56]). The results suggest that cognitive remediation is cost-effective at post-treatment and that this therapy can be delivered at no additional cost compared to usual care alone. These results are promising but more studies are needed which measure these types of outcome.

Conclusion

In the early 1990s the aim was to develop new treatments for enhancing cognition in people with schizophrenia. Several years of research suggest that it is possible to enhance cognitive functioning in people with schizophrenia [25]. Identifying the moderator and mediator variables in the efficiency of cognitive remediation is the main challenge for the future. Such underlying mechanisms in longitudinal studies can also inform us about the clinical characteristics of the disease [48]. Effective cognitive remediation therapy may also be used as a preventive strategy in schizophrenia and offered to people who are at high risk of developing psychosis or of exhibiting cognitive functioning problems. This could be an interesting avenue to pursue in building a risk disease model.

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Chapter 11
Individual Psychotherapy for Schizophrenia: An Overview of Its History, Recent Developments and New Directions

Paul H. Lysaker and Molly A. Erickson

Abstract Empirical study of long term outcomes for persons with schizophrenia suggests that recovery is often possible. This literature also emphasizes that recovery may involve different kinds of experiences for different people with the same psychiatric condition. For some, recovery may mean symptom remission while for others it may be reflected by the achievement of psychosocial milestones. For yet others, however, to recover can involve subjective changes in how those persons experience themselves as meaningful agents in the world. For some, to recover could be to reclaim a full sense of self, a sense of self that can meaningfully engage others and the rigors of daily life. In this chapter we review the potential of individual psychotherapy to address the more subjective aspects of recovery related to sense of self. We first review literature on the effectiveness of psychotherapy for persons with schizophrenia. We then discuss literature on the larger issue of how decrements in personal narrative and metacognition may underpin some of the disturbance in sense of self observed in schizophrenia. Finally, we focus on how psychotherapy could be conceptualized and adapted to help enrich self-experience by addressing narrative and metacognition. Directions for future research are discussed.

Keywords Schizophrenia · Psychotherapy · Recovery · Narrative · Metacognition · Recovery · Psychosis · Quality of life · Self

Abbreviations

CBT	Cognitive behavior therapy
SAMHSA	Substance abuse and mental health services administration
STAND	Scale to assess narrative development
MAS	Metacognition assessment scale

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Only a few decades ago, schizophrenia was widely believed to represent a life-long illness with a poor prognosis. Persons with schizophrenia and their families were told by mental health providers that the best realistic outcome would be stability or absence of negative events and states such as hospitalization, incarceration, or gross inactivity. The idea that a person with schizophrenia might lead a normal and fulfilling life seemed beyond the bound of possibility. As detailed by an increasingly large number of studies, this view has proved to be inaccurate at best, and destructive at worst [1–3]. Large scale cross-sectional and longitudinal studies have revealed that most people with schizophrenia commonly do much more than remain stable. More often than not, persons move toward or achieve a meaningful form of recovery over the course of their lives [4].

Importantly, as clinicians, researchers, and persons with schizophrenia have tried to systematically study and describe recovery, they have noted that achieving wellness in the face of schizophrenia is a highly complex process composed of many different facets [5]. For some, to recover or to thrive again may mean being able to work again or to have fewer symptoms of psychosis or depression. For others, recovery may mean finding stable housing, recapturing enthusiasm for a hobby, or falling in love. Beyond these objectively verifiable definitions, and of central importance to this chapter, recovery may involve persons finding a way of again experiencing themselves as individuals with a rich history and potential to influence their own futures, regardless of reductions or increases in dysfunction or symptom severity [4, 6, 7], As Kean [8], someone who has experienced the illness herself, has described:

> What lies behind the symptoms is a tormented self, a highly personal experience unchangeable and irreplaceable by any physical treatment… [D]espite the "usual" voices, alien thoughts and paranoia, what scared me the most was a sense that I had lost myself, a constant feeling that my self no longer belonged to me. This has nothing to do with the suspicious thoughts or voices; it is purely a distorted state of being. The clinical symptoms come and go, but this nothingness of the self is permanently there (p. 1).

Considering the experience that Kean has described here, it is plain that recovery for some persons involves things which are not related to symptom remission or even level of social function. Instead, recovery may involve emerging from a state in which the self has been experienced as lessened in terms of vitality and agency, sometimes to the point of persons feeling a near void in place of where there had been a core sense of self [9–13]. Growth in the domain of self-experience may represent, in one sense, a more personal process wherein persons recognize their ability to direct their own recovery and thereby to attain other goals, such as forming deeper bonds with others, returning to work, or pursuing a college degree [14].

One issue raised by the recognition that recovery may involve such deeply subjective phenomenon pertains to how a treatment might assist with such a process. Empirically supported psychosocial interventions are available which improve outcomes in schizophrenia. Interventions such as social skills training [15], family psychoeducation [16], and illness management and recovery [17] are widely

available and can assist persons to learn new ways to cope with many of the difficulties posed by mental illness and therein clear the way for new opportunities to arise. These interventions nevertheless tend to focus on skill acquisition and the resolution of specific problems. As such it is not clear that they in their current form would necessarily help persons to solve the dilemma described by Kean above. Of note, this is not to say that they might not assist with subjective elements of recovery, indeed they may; this is only to point out that skills-based treatments do not seem to include any explicit elements which focus on self-experience.

In the present chapter we accordingly plan to focus on the possibility that individual psychotherapy, a treatment which involves explicit attention to self-experience may assist with the recovery of aspects of self-experience. We will consider the possibility that individual psychotherapy may be a potentially helpful and often underutilized treatment option for people with schizophrenia who frequently experience a diminished sense of self. One basis for exploring this is that psychotherapy has helped a wide range of people without psychosis to develop both a richer sense of self and a more adaptive self-concept [18, 19]. Furthermore, others who have successfully delivered treatments focused on symptom remission have also noted the benefits of moving from symptom-focused to person-focused treatments that attend to the subjective development of the sense of self [20, 21]. Of note, we are not referring here to an interest in resurrecting a psychotherapy that looks for the roots of schizophrenia in psychological conflict or one that places persons in a passive patient role wherein others identify and solve their problems for them. We instead raise for discussion whether an individual psychotherapy could help recovering persons cultivate a richer, consensually valid and more positive sense of self across a range of life experiences.

Importantly, individual psychotherapy, though absent from most discussions of recovery focused treatments, is still commonly offered in a range of programs [22]. It often takes the form of a supportive relationship which is not entirely distinguishable from a friendship, and includes a weak (at best) focus on the quality of the patient's internal experience. Thus our wish is to not only explore the role of psychotherapy in terms of promoting recovery but also to move towards a more precise account of what is involved in the recovery of self-experience.

To accomplish this, the following discussion is accordingly divided into four sections. In the first we discuss evidence for the effectiveness of psychotherapy for persons with schizophrenia as well as comment on some of the historical factors which have previously served as a barrier to the inclusion of psychotherapy as part of the treatment regimen. Next we explore the nature of alterations in self-experience in schizophrenia, focusing on how disturbances in personal narrative and metacognitive capacity could underpin these difficulties. Third, we will focus on the conceptual basis for the role of psychotherapy in promoting aspects of recovery. Here we describe two different, but related, processes relevant to the recovery of self experience: the development of personal narrative and the capacity for metacognition (or thinking about thinking). In the final section we discuss promising directions for future research.

A Brief History of the Psychotherapy of Schizophrenia

One of the first clinicians to seriously advocate for individual psychotherapy for people with schizophrenia was Carl Jung [23]. Jung treated many hospitalized and severely ill patients in the early part of the twentieth century and, contrary to the prevailing wisdom at that time, argued that psychotherapy could assist persons with schizophrenia to make sense of what was happening in their lives, to form a richer idea of who they were as human beings. Initially, Jung seems to have been alone in this pursuit. Freud [24] asserted that psychoanalysis with people with schizophrenia was impossible. In his view, persons with schizophrenia had withdrawn all interest from the world and as such could not form a sufficient attachment to the therapist – therefore, none of the key interpersonal processes on which psychoanalysis is based could occur. Even so, by the 1940s, interest in psychotherapy for schizophrenia suddenly appeared in a range of different settings. Fromm-Reichmann [25], Hill [26], Searles [27], Sullivan [28], and Knight [29] all reported that they had meaningfully engaged in some form of psychoanalytic psychotherapy with schizophrenia patients. Based on their experiences, they contended that meaningful and intimate bonds with patients could, in fact, be formed. They also noticed that patients with this condition were commonly eager for treatment and were able to utilize the therapeutic relationship as the basis for some form of recovery. These and other authors produced a wealth of compelling anecdotal reports suggesting that persons with schizophrenia could accept and embrace psychotherapy as a means to make sense of their lives in a holistic manner.

Psychoanalytic psychotherapy for schizophrenia thus emerged as a treatment geared towards helping patients to develop a healthier sense of themselves by making use of the therapeutic relationship. From the psychodynamic perspective, schizophrenia might result from early relationships with caretakers and the development of a primitive array of defenses [30]. Importantly, symptoms of schizophrenia such as paranoia, blunted affect, and catatonic behavior are viewed either as defense mechanisms against feelings of fear, rage, or inadequacy [27] or as a failure of internalization early in life leading to a fundamentally weak self organization [31]. Erratic behavior and poor communication skills between the patient and therapist in this context was potentially seen as the repetition of prior relationships with parents and siblings. As such, a large portion of the insight-oriented therapy is focused on the therapeutic relationship with the purpose of eventually breaking down the patient's maladaptive responses to an unsettling environment.

While this literature produced a series of interesting though sometimes internally inconsistent theories of the subjective experience of psychosis and its antecedents, there was little scientific evidence supporting its efficacy. As reviewed in several sources, randomized controlled trials failed to find significant benefits for psychoanalytic psychotherapy [32–38]. For instance, in what is known as the Boston Psychotherapy Study, over 160 adults with schizophrenia were randomly assigned to receive psychoanalytic insight-oriented therapy or a reality based supportive psychotherapy [39]. In this study, insight-oriented therapy aimed to use the therapeutic relationship as a space for exploring the patient's inner experiences, including

unconscious desires and motivations, self-understanding, and feelings and conflicts. Patients assigned to this group met regularly with their clinicians for approximately 2 years. Extensive efforts were devoted to the training of therapists, the selections of appropriate participants, assessment procedures and methods. Nevertheless, at the 2-year follow-up assessment there was no consistent or significant difference in outcomes between the group of patients receiving psychoanalytic treatment and those receiving supportive psychotherapy. In fact, the most notable result from this study was an attrition rate of just over 40% 6 months after treatment assignment, and an attrition rate of nearly 70% at the 2-year follow-up. More detailed analyses of the results of those who remained in the study revealed some improvements in insight as well as improvements in negative symptoms among participants assigned to the more skilled therapists [39, 40].

Following this, and concurrent with the recognition of recovery as a likely outcome of schizophrenia, a range of new possible rationales for psychotherapy for schizophrenia have been raised as well as empirical support for the efficacy of psychotherapy. Perhaps most prominent among these involve cognitive behavior therapy (CBT). Originally created to address depression, the use of CBT has steadily expanded to address schizophrenia and other psychotic disorders [41]. Treatment from this perspective has stressed that symptoms can be addressed in cognitive terms, that is, as they are reflective of and sustained by maladaptive and inaccurate beliefs. CBT seeks to correct those beliefs through a systematic, collaborative process of belief examination, as well as prediction of the consequences of behaviors and events.

Evidence supporting the efficacy of CBT includes randomized controlled trials showing that persons with schizophrenia can accept CBT, and that CBT can reduce dysfunctional cognitions, positive and negative symptoms, and promote improvements in psychosocial function. For example, Drury and colleagues [42] observed that individuals with non-affective psychosis endorsed fewer delusional beliefs and exhibited significantly less severe positive symptoms at the conclusion of a 6-month cognitive therapy treatment program compared to patients who received nonspecific supportive therapy. This improvement in symptomatology was maintained at a 9-month follow-up assessment. Lysaker and colleagues [42, 43] reported that participants offered work placements who were randomly assigned to receive CBT as opposed to supportive psychotherapy worked more hours and demonstrated better work performance over a 6-months trial. In a follow-up intensive case study which attempted to understand the therapeutic methods it was suggested that CBT may help persons first recognize their thoughts as thoughts and then to change beliefs leading to changes in behavior and better function in interpersonally stressful work settings. Sensky and colleagues [45] found that symptom severity declined equally for patients receiving CBT and for patients receiving a nonspecific befriending intervention; however, unlike the control group, the group receiving CBT continued to improve in symptom remission after the conclusion of the treatment program. Similarly, Gumley and colleagues [46] found that patients randomized into a CBT treatment group not only demonstrated improvement in symptom severity, but also improvement in social functioning and reduced relapse rate compared

to a treatment-as-usual group. One meta-analysis conducted by Pilling and colleagues [47] indicated that CBT appears to consistently and significantly improve important indicators of mental health, such as positive symptoms and insight into one's mental illness. However, the authors of this study noted that CBT does not appear to consistently reduce relapse rates or improve global functioning across studies.

Diverging slightly from this line of thought, Chadwick [20] developed Person-Based Cognitive Therapy for psychosis, in an effort to move from a symptom-focused to a person-focused therapy. Person-Based Cognitive Therapy is an integrative form of treatment which draws on cognitive theory, mindfulness, client-centered approaches, and a social-developmental perspective which conceptualizes language as a socially available tool which persons use to make meaning of their daily activities. This approach uses cognitive and experiential techniques for working with pervasively negative self schemata and promoting self-acceptance and self-awareness. Case studies by other authors have also suggested some forms of cognitive behavior therapy for psychosis can address the personal meaning of symptoms and psychosocial dilemmas leading to symptom reduction and improved community function [47, 48].

Of note, concurrent with a wealth of interest in CBT, interest has also increased in using a modified form of psychoanalytic therapy for people with schizophrenia. Bachmann and colleagues [49] have suggested that psychoanalytic psychotherapy for people with schizophrenia may beneficially foster an experience of the self and the therapist as two separate people that share a relationship, leading to the stabilization of a sense of personal identity, and the integration of the psychotic experience. Some evidence suggests that such an approach can be helpful, at least for people who are more clinically stable at the outset of treatment [50]. Rosenbaum and colleagues [51] have indicated that among first episode patients, those who received supportive individual psychodynamic psychotherapy or an integrated treatment had better overall functional outcomes after 1 year of treatment than those who received treatment as usual.

Schizophrenia and Sense of Self: Related Links with Narrative and Metacognition

Before turning to the issue of the potential of psychotherapy to address the recovery of sense of self in schizophrenia, it seems important to comment at least briefly on the processes involved in self-diminishment – that is, the processes that may be the treatment target for psychotherapy. For the sake of clarity we will label the central dilemma to be overcome, as "self-diminishment". Consistent with the description of Kean above, authors ranging from Bleuler [52] to Laing [53] to Stanghellini [54] and from Searles [27] to Davidson [6] have described persons with this condition as experiencing their vitality, their core sense of being as somehow having become less, or diminished from what it was previously. Each of these writers in their own

way paints a portrait of the illness in which there is a loss of oneself as the director, actor and narrator in one's own life.

Considered through the lens of contemporary research, the experience of self-diminishment can be conceived of as involving two interrelated processes. First, from the larger frame, reductions in sense of self may be related to alterations in personal narrative. By personal narrative we refer to the possession of an evolving and storied sense of one's life, that is, an account of oneself over time and not collection of facts. To have a personal narrative is to have a temporal sense of oneself as a being with some consistency across events, as a being who acts as an agent in the world and who is moving towards any of a number of possible futures. As noted by Bruner [55], narratives are not accidental byproducts of life but the means by which persons make meaning of their experiences.

As described by Lysaker and Lysaker [14] as well as others [56], personal narratives emerge from an ongoing dialogue between others and within oneself, and give coherence to one's goals and behavior over time. It is argued that individuals primarily exist in a world of dialogues, and form a sense of self (i.e., self-as-daughter, self-as-success, self-as-victim, etc.) on the basis of these continual dialogues; thus, a cohesive, albeit complex and occasionally contradictory, personal narrative emerges over time and guides future behavior. Qualitative analyses have suggested that diminished sense of self in schizophrenia may reflect disruptions in the process by which these dialogues are carried out [57, 58]. If the ability to sustain these conversations with others and within one's self is compromised, there may be a loss of the evolving self-experience that is the core of a personal narrative.

There are at least three ways in which this dialogue may become compromised: First, ongoing dialogue may relatively cease, resulting in a self-experience that is barren or empty. In such cases the individual's personal narrative may be poorly developed and unembellished, consisting of only a few fragmented thoughts, feelings, and memories. Second, dialogue may continue but exist only in an inflexible state, leading to a personal narrative that is rigid, repetitive and without nuance. Finally, the dialogue may persist but be disorganized to the point that it is nothing more than a cacophony of thoughts, feelings and goals without meaningful links to life events. In such a condition, the potential for coherent narrative is lost, replaced by a rapid and chaotic succession of self-experiences. This leads to an incoherent personal narrative filled with abstract generalizations and preoccupations that appear to be divorced from reality.

In this sense, a disturbance in the continuity of personal narrative is a likely candidate for a cause of the kinds of self-diminishment Kean and others have described. Without a sense of one's own story, the events of life unfolding in the moment would naturally seem less interpretable and suddenly difficult to engage and a person might well experience their core identity as somehow lessened. With no idea of how the person one is today is linked to the person one was years ago, it might well be experienced that the stuff of one's own being had been eroded. In support of this are recent findings confirming schizophrenia may be linked to a loss of the coherence of personal narrative [59, 60] and that persons with less rich narratives tend to have

poorer social function independent of other more cognitive factors including beliefs linked to hope and self-esteem [61].

From a smaller, more focused frame, diminishments in sense of self may be related to diminishment in metacognitive capacity. The term "metacognitive capacity" refers to the ability to think about thinking [62]. An act of metacognition would involve a situation in which someone considers their own thoughts or the thoughts of others. Examples of different kinds of metacognitive acts might include forming ideas about what other people are thinking and feeling on the basis of visual or verbal cues, using knowledge about oneself to find a new solution to a psychological problem, or perhaps simply uncovering an emotion one is feeling which underlies an urge to do or say something. By referring to metacognition as a "capacity" we are furthermore referencing a dimensional construct along which persons can vary in terms of their abilities to perform increasingly complex acts of metacognition. Someone with lesser capacity might be able to only perform metacognitive acts at more basic levels (e.g. recognizing that the thoughts in one's head are one's own) while persons with greater capacities might be able to perform more complex acts (e.g. identifying a pattern in how thoughts and feelings are connected over time).

Just as developing a personal narrative gives coherence to one's life over time, metacognition makes internal experience, both one's own and that of others, interpretable. Thus, to lose any portion of this capacity might be experienced as the loss of one's self, and one's understanding of relationships with others. If it were to suddenly become more difficult to detect thoughts and feelings, it seems plausible to suppose that an individual might sense a decrement or diminishment in terms of the substance or intensity of one's self. In support of this hypothesis is two decades of literature suggesting that persons with schizophrenia experience deficits as a feature of the mental illness [63]. For instance, many persons with schizophrenia have difficulty forming ideas about what other people are thinking and feeling on the basis of visual or verbal cues, recognizing themselves as the source of some of their own thoughts and actions, and developing a coherent account of their own mental states [14, 64–69]. These deficits appear to be relatively stable over time and, while correlated with severity of psychopathology, are not simply the byproducts or reflection of symptoms or other clinical features of schizophrenia [70–73].

Of note, an impairment in metacognitive capacity should negatively affect the ability to recognize oneself as a distinct agent in the world, both in the moment and across time. This ability is of central importance if one is to create, share, and revise a rich and complex personal narrative [74]. In this sense, deficits or limitations in narrative and metacognition ought to affect one another in the manner of a vicious circle. With difficulties in the act of thinking about thinking should come impoverished narratives; and with impoverished narratives there should be little to contemplate and thus less metacognitive activity. Consistent with this supposition, at least one study has suggested that deficits in metacognition are linked to impoverished narratives among persons with schizophrenia [75].

Addressing Narrative and Metacognition within a Psychotherapy for Schizophrenia

If diminishment in self-experience is driven by deficits in narrative and metacognitive capacity then it might be possible for psychotherapy to promote recovery by addressing both in an interlocking manner. First, psychotherapy could offer a conversation or dialogue that might revitalize the processes by which a narrative is produced. For example, an individual with schizophrenia whose dialogue has relatively ceased might be prompted to recount his experiences raising children, attending high school, or disagreements with siblings. In this way, he might begin to expand on his barren narrative by taking on perspectives such as self-as-father, self-as-student, and self-as-brother. As therapy progresses, more nuanced perspectives might be elicited, such as seeing oneself as a victim or as someone who triumphs in the face of adversity, all leading to the development of a richer story of one's life. In this approach the person might first collect and rediscover lost details of their lives, arrange those details in a temporal order and then form, from the position of an author, the larger story of their own life. Rather than focusing on the validity of an individual's conclusion or his response to a particular symptom, a narrative-focused approach might thus lead him to develop a richer and more complex story about who he is in the present, who he has been across the course of his life, and what possibilities to which he may yet aspire.

In line with the SAMSHA [5] principles of recovery, a deepened personal narrative naturally provides an opportunity for one to experience oneself as an active agent who can influence his or her own recovery. Again, whereas symptom- or problem-focused approaches might help individuals move past specific hurdles, the targeting of personal narrative could specifically address the lost sense of diminished self described by Kean [8]; the complex and nuanced understanding of oneself that results from this type of approach may then generalize to a range of future challenges. Preliminary evidence indicates that this is, in fact, the case: quantitative case studies of people with schizophrenia have suggested that improvements in the richness of personal narratives can emerge over several months of individual psychotherapy, and that improvement in personal narratives are linked with reductions in positive symptoms and the ability to make sense of daily experiences [76, 77]. Other studies have suggested that self-concept is a meaningful predictor of outcome in a range of other domains such as symptomatology and social functioning in both first episode [78] and more advanced phases of illness, regardless of the etiology of difficulties with narratization [79].

The second related approach to addressing impoverished self-experience in schizophrenia involves developing enhanced capacity for metacognition. From this perspective, treatment can help individuals with schizophrenia develop the capacity to form increasingly complex representations of their own thoughts and the thoughts of others. Each individual session can therefore be an opportunity to practice metacognitive acts. Whereas from the narrative perspective persons might

discover and elaborate upon details about their lives, here we envision a psychotherapy that might simultaneously help persons to recognize their thoughts as their own, to distinguish affects, and eventually doubt and reform conclusions. Put another way, the narrative approach to individual psychotherapy encourages the development of a macroscopic representation of a life within which the self abides. By contrast, the metacognitive approach encourages development of the self on a microscopic scale, addressing the atoms of experience that make up a "self" such as thoughts and emotions.

As an illustration, consider the example above of the person with barren narrative. Psychotherapy from the metacognitive approach might help this person tease apart and examine the thoughts they are having in their mind. As therapy progresses, it might help the person to next realize that some of these thoughts are memories which involve different emotions. With time the person may come to realize that they have formed conclusions which can be altered, all of which ultimately culminate as an experience of the self.

As noted by Choi-Kain and Gunderson [18], there already exist a number of psychotherapies which have demonstrated in empirical studies the potential to improve metacognitive capacity in individuals with other types of mental illnesses, the most notable of which are borderline and other personality disorders [80–82]. Metacognition-based approaches appear to be particularly useful for personality disorders, as persons with these conditions are frequently characterized as experiencing chaotic and dysregulated patterns of thought and emotion [83]; in fact, detailed case studies have revealed that gains in metacognitive capacity for these patients over the course of therapy are associated with improvement in quality of relationships, emotion regulation, and vocational outcome [83, 84]. In addition to individuals with personality disorders, improvements in metacognition over the course of psychotherapy have been documented in empirical studies for a variety of Axis I mental illnesses such as anxiety, depression, substance abuse, and eating disorders. Furthermore, these improvements in metacognitive capacity were related to reductions in the severity of psychopathology [85, 86].

Given the preliminary evidence for success in improving metacognition and symptomatology in a variety of mental illnesses, it is reasonable to conclude that these procedures may be adapted to address the lost or fragmented sense of self frequently reported in schizophrenia [8]. Indeed therapy could potentially be structured to aid in the recovery of metacognitive capacity and personal narrative by providing a space in which such skills can be practiced and exercised with increasing degrees of complexity, beginning only with what the person is capable of performing. In this way, psychotherapy could be framed as a process akin to physical therapy, which aims to cultivate the capacity to re-engage in physical activity that patients were once able to perform; similarly, if it can be inferred that metacognitive capacity atrophies with the onset of mental illness, it may be regained by providing opportunity to practice it. Following the metaphor of physical therapy, it may be noted that practicing these skills that might have been dormant for years is difficult and sometimes painful. However, with improvements in metacognition, a more complex personal narrative might follow and a sense of self may begin to re-emerge.

Beyond the theoretical impetus for introducing a metacognitive approach to psychotherapy for individuals with schizophrenia, there are now several lines of evidence suggesting that significant improvement in metacognition is possible in these patients. For instance, case studies have revealed significant improvement in metacognition for individuals with schizophrenia over the course of therapy [76]; furthermore, such improvements in metacognition have been linked to decreases in the severity of delusions and impairments in insight [21]. In addition to studies that evaluate the outcomes from metacognition-focused treatment, there is also evidence that metacognition tends to improve with other types of treatment as well. In one particular study of the effects of cognitive remediation on attention, executive function, and working memory deficits in schizophrenia, Spaulding and colleagues [87] discovered that the primary gains involved not improvements in basic cognition, but rather an increased ability to flexibly engage in problem solving strategies. Furthermore, many versions of Cognitive Behavioral Therapy for psychosis [88] incorporate activities related to enhancing metacognition, such as identifying pervasive errors in logic and misperceptions as core components of the treatment. In a similar vein, it has been demonstrated that training in social cognition may improve theory of mind, which is considered similar to metacognition, as well as reducing attributions of hostility in others for people with schizophrenia [89]. Finally, Chadwick [20] has indicated that promoting metacognitive insight is a core goal of Person-Based Cognitive Therapy for severe mental illness. Metacognitive approaches within this therapy address the meaning of symptoms, internal experiences, negative self-schema, and the conceptualization of oneself as a complex, sometimes contradictory, and continually evolving agent. Chadwick [20] describes methods for achieving these goals, and interested readers are directed to the sample therapy transcripts that are available documenting the ways in which this therapeutic approach proceeds.

In summary, we suggest that there are at least two ways in which psychotherapy could target the diminished sense of "self" in schizophrenia. First, psychotherapy could promote the recovery of a fuller sense of self by offering a forum within which individuals may cultivate and expand upon their own personal narratives. Through psychotherapy persons might reclaim a sense of themselves as linked to a unique past and as moving towards a number of possible futures. With a renewed understanding of life events as unfolding in a manner that makes sense, the person might again see himself or herself as an agent in a world that is once again fully coherent and viable. Second, psychotherapy could help persons become better able to think about their own thinking. By the processes of exercising metacognitive capacities in psychotherapy a person might become better able to experience their thoughts as their own, develop a nuanced sense of their own emotions and tendencies to reach maladaptive conclusions. With better metacognitive skills and a developed personal narrative, one's experience of the "self" is no longer meaningless fragments, and a coherent understanding of day-to-day life events once again emerges.

Future Research: Three Related Foci

As we have argued thus far in this chapter, a promising body of literature has emerged which indicates that (1) lost or deteriorated sense of the "self" is a common feature of schizophrenia, (2) recovery of sense of self can be achieved, and (3) approaches to psychotherapy that address personal narrative and metacognition are possible for patients with schizophrenia and appear to be effective in ameliorating symptom severity. Given the potential for psychotherapy to address these subjective aspects of recovery, an important area of future inquiry will be in the development of manualized treatment protocols. In these it will be essential that the key elements of a recovery focused psychotherapy be details which will allow formal research to test the feasibility and effectiveness of these methods in randomized controlled trials. We envision a manual for this approach to psychotherapy that addresses both narrative and metacognition deficits, as these two facets of self-experience are fundamentally interdependent. Without metacognitive ability it should be nearly impossible to create a comprehensive and nuanced personal narrative; similarly, without a sense of one's life narrative there should be little demand for complex acts of metacognition.

Regarding personal narrative, a future treatment manual ought to provide a flexible outline that clinicians can use as a guide for eliciting a complex and multi-layered narrative over the course of therapy. Keeping in mind that narrative development will not necessarily follow the same course for all patients, we suggest that a core feature of the narrative-based intervention should involve the simultaneous development of a number of semi-independent stories, which ought to be unique to each individual. Such stories might include facing personal challenges, experiencing success, experiencing failure, feeling grief over losses, and setting goals for the future. Importantly, this type of intervention features the deeply personal and subjective experience of the self; discussion of the person's symptoms of mental illness and accompanying challenges should not be attributed to or dismissed as an exclusively biological phenomenon. Rather, when discussion of these symptoms and challenges arise, they ought to be explicitly linked to the patient's developing personal narrative in a way that is both valid and preserves self-esteem. Over the course of therapy, then, it is expected that a unique personal narrative will emerge that is able to comprehensively integrate these semi-independent stories from the past and guide future thoughts, goals, and behavior.

Regarding the metacognition facet of the intervention, a future treatment manual may serve as a guide for clinicians as they use therapy to provide a place in which clients may exercise their capacity to think about thinking. We envision this portion of the treatment protocol as an opportunity for patients to practice acts of metacognition with increasing levels of complexity with support and guidance from the clinician. Therapy can thus be used as a space to examine and monitor attributions regarding self and others, symptoms and mental states, schemata-linked patterns in thinking and behavior, and the patient's thoughts and feelings about his or her self. As is the case with addressing the personal narrative, changes in metacognition over the course of therapy will be different for each individual, and each individual

will enter into therapy with a different level of metacognitive capacity. For some patients who are very limited in metacognitive ability at the time that they enter into treatment, interventions will involve understanding that the thoughts in one's head are one's own, observing that others have unique thoughts and motivations that are distinct from one's own, and recognizing that one has a psychological problem (such as a mental illness). For many other patients, metacognitive interventions can begin at a higher level, such as recognizing emotions associated with thoughts and life circumstances, interpreting others' behavior, and forming links between one's behavior and one's psychological state (for elaboration on this process, see Lysaker and colleagues [90]). A treatment manual that incorporates metacognition-based approaches would, therefore, need to be versatile such that it could be used for a broad spectrum of baseline ability.

Related to the need to develop a treatment manual is the question of which assessment tools can be used to evaluate changes in the sense of self promoted by the intervention. There are already many different types of instruments in existence that are commonly used to assess various aspects of outcome in schizophrenia such as symptoms, life satisfaction, hope and self-esteem [7, 91]. Beyond these, efforts have recently been undertaken to develop a more proximal measure of changes in self-experience over the course of therapy. The Scale to Assess Narrative Coherence (STAND [92]) is now available to rate the extent to which a coherent and complex personal narrative arises in spontaneously generated speech samples (e.g. from psychotherapy transcripts or in semi-structured interviews). Specifically, the STAND assesses the degree to which individuals describe themselves as someone with social worth, being connected to others, and having the ability to meaningfully influence their own future – elements of recovery that are all closely tied to the SAMHSA [5] principles of recovery. Still other methods are being developed which assess different aspects of metacognition [64]. These include both laboratory tests as well as rating scales such as the Metacognition Assessment Scale which can be used to determine the extent to which persons are capable of engaging increasingly complex levels of metacognition. Inter-rater reliability, internal consistency and concurrent validity have been established for both the STAND [93] and the MAS [94] in several samples of adults with schizophrenia in non-acute phases of illness.

With the advent of new instruments that can assess changes in personal narrative and metacognition throughout the course of therapy, other important practical and theoretical issues are likely to present themselves as subjects for future research. For example, if the proposed set of narrative and metacognition-oriented procedures receives general empirical support in independent replication, it will become increasingly important to learn how to implement the treatment in the wide variety of mental health settings available for patients with schizophrenia. What sorts of training and supervision will be needed? What environmental variables affect adherence to the treatment protocol? Furthermore, along what kind of time frame should different forms of improvement be expected?

In addition to the development and systematic assessment of a manualized treatment, a second, more theoretical target for future research involves investigating changes in narrative and metacognition that accompany other types of treatment

currently being used in mental health clinics. With the development of new assessments such as the STAND and the MAS, it is now possible to empirically examine the reciprocal relationship of personal narrative and metacognition development with functional assessments of vocational, interpersonal, and community function. Such investigations would not only be of theoretical importance in terms of conceptualizing the process of recovery and describing the constructs associated with personal narrative and metacognitive capacity, but it may also assist in the development and refinement of new and more effective treatments. Ultimately, such a program of research can systematically compare the ways in which the various treatments aimed at recovery of sense of self in schizophrenia can improve personal narrative and metacognitive capacity, and can explicate the relationship between improvement in these subjective domains and other, more objective measures of recovery such as symptom remission, hopefulness, and improved quality of life.

In practice, it has been observed that participation in rehabilitation appears to reshape the ways in which one makes meaning of one's life, both in the short- and long term [95]. Such evidence underscores the importance of evaluating the narrative- and metacognition-based therapeutic effects of treatments that stress the benefits of environmental support systems. For example, it will be of interest to examine whether the acquisition of skills and the cultivation of natural support systems in other evidence-based programs have similar or different therapeutic effects compared to the proposed treatment protocol that directly targets personal narrative and metacognition development, specifically. Such a program of research may lead to insights that further enhance the therapeutic effects of these interventions. This line of inquiry may also lead to important developments with regards to the interface of narrative- and metacognition-based psychotherapy and other types of interventions, which may lead to more effective combinations of treatment strategies. For example, it may be that cognitive remediation, which aims to improve cognitive flexibility, can augment the impact of psychotherapy and shorten the time frame for recovery. In a similar fashion, it may be that vocational rehabilitation in conjunction with recovery-oriented psychotherapy may provide a more potent context for individuals with schizophrenia to develop and expand upon their personal narrative [96, 97]. Though these hypotheses warrant further study, there are promising avenues of inquiry that integrate the proposed individual psychotherapy with other types of critical interventions.

A third and final focus for future research may address the question of whom might benefit the most from the proposed approach to psychotherapy. For instance, it would be important to determine whether this type of intervention is best suited for individuals with a recent onset of mental illness, or for individuals who are at a later stage in their illness. Intuitively, it appears that individuals with recent onset of mental illness have many difficult things that must be integrated quickly (i.e., the meaning of the recent psychotic episode as it pertains to their life trajectory, interpreting the illness as an obstacle to overcome or evidence of inevitable decline, whether life dreams must be abandoned, etc.). For this patient, a therapy that addresses issues of personal narrative and metacognition may be uniquely useful. On the other hand, individuals who are at a later stage of their illness may

similarly benefit from this type of intervention, though their needs may be different from someone with a recent onset. For this patient, large gaps of time may have passed unnoticed by the individual during a severe episode, leaving a sense of loss that must be addressed as the patient attempts to regain a sense of control over his or her own future. It has been suggested that the needs of older individuals with schizophrenia are still not well understood and often go unaddressed [98]. Thus, narrative- and metacognition-based approaches may potentially be valuable for both types of patients, but perhaps in unique ways.

In addition to duration of illness, there are several other individual factors that may make the proposed type of psychotherapy more appropriate for some patients than for others. For example, cognitive ability and the related socio-economic status of the patient may influence the rate at which change can be expected in the metacognitive- and narrative-based approach to psychotherapy. It is not yet clear whether patients with higher levels of premorbid function may improve more rapidly with individual psychotherapy than individuals who had lower levels of premorbid function. Again, these individual characteristics of patients warrant future study in evaluations of treatment effectiveness.

Summary and Conclusions

Recent changes in the conceptualization of recovery have given rise to a renewed interest in the role of psychotherapy for treatment of schizophrenia. To explore this issue we have described the evolution of the use of psychotherapy to target diminished sense of self in schizophrenia; we then reviewed evidence indicating that impoverished sense of self, which is a potent barrier to recovery, can be targeted and improved with psychotherapy. In particular, we have suggested that psychotherapy can address the interrelated facets of self experience, personal narrative and metacognition, by providing a space for clinicians and patients to explore and exercise the skills necessary for a more complete, complex, and integrated sense of self. With the attainment of a richer personal narrative and greater capacity to think about thinking, evidence indicates that individuals with schizophrenia may feel sufficiently empowered and able to envision a hopeful future. In contrast to symptom- or problem-focused approaches, addressing these large-scale skills necessary for a rich self-experience may enable individuals with schizophrenia to adaptively formulate solutions to future challenges, and to withstand threats to self-esteem and hopefulness about the future. By targeting the underlying skills, this approach may lead to a sustained sense of wellness and assist persons to be in a better position to both preserve hope and make reasoned decisions in the face of adversity.

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Chapter 12
An Overview of Cognitive Behaviour Therapy in Schizophrenia Spectrum Disorders

Kieron O'Connor and Tania Lecomte

Abstract Cognitive behaviour therapy (CBT) has become a treatment of choice for several schizophrenia spectrum disorders. This chapter traces the development of CBT from early attempts at thought stopping to more recent developments of cognitive therapy specialized for psychosis. CBT strategies have drawn on information processing biases such as threat bias, attentional bias, reasoning bias, data gathering bias, externalizing bias, lack of agency, and intention initiation. Meta-analytic reviews of the efficacy of CBT in psychosis have shown strong effect sizes when compared with no treatment but less strong when compared to supportive therapy, and proportions of clinically significant change have often not persisted between CBT and comparison therapies at follow-up. Although current CBT programs share common theoretical foundations and follow a similar format of preparation, restructuring and reality testing, experimental findings and clinical strategies differ for specific spectrum disorders. In addition, CBT programs have been tailored to specific stages of development, such as early onset or relapse prevention. There is also a trend towards limiting the targets of CBT intervention to focus on alleviating specific features such as emotional distress, or level of beliefs, or degree of preoccupation, rather than addressing core beliefs. Further challenges for CBT include improving access to and treatment delivery of CBT to diverse populations and through diverse professions. There have recently been attempts in UK and elsewhere to set up pyramid training and to encourage community settings to implement best practices. Alternative treatment delivery involves group formats and new technologies including computer and teleconferences following step care models.

Keywords Cognitive behaviour therapy · Psychosis · Positive symptoms · Negative symptoms · Clinical trials · Treatment delivery

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Abbreviations

APA	American Psychiatric Association
CBT	Cognitive behaviour therapy
COPE	Psychosocial interventions for psychosis pathways
SCIT	Social cognition and interaction training
SoCRATES	Study of cognitive reality alignment therapy in early psychosis

Overview

Schizophrenia spectrum symptoms are generally divided into positive symptoms including hallucinations and delusions, and negative ones including anhedonia, loss of interest, energy and incentive and social isolation. Positive symptoms may also extend to schizotypic and dissociative states such as depersonalization, found outside of schizophrenia itself. Since the first trials of CBT for schizophrenic symptoms [1–3], there has been continuous support for its efficacy as a frontline treatment, especially for positive symptoms. CBT continues to show an efficacy not paralleled by any other treatment so far. It is also 7 years since the UK National Institute of Clinical Excellence [4] recommended, in 2003, that all psychotic patients receive some form of CBT. Hence, Tarrier and Wyke [5], in an influential review, conclude that of course CBT is effective but they add cautionary tales. The caution that Tarrier and Wyke [5] note refers to accurate effect sizes and effective implementation of CBT. But since the early days of CBT success, a number of issues have been raised considering CBT use in schizophrenia spectrum which we will review in the current chapter.

These issues include: defining useful components of CBT, integration of CBT with other therapies, and in particular the role of emotional interventions such as befriending empathy and social support; the extension of CBT for dealing with negative as well as positive symptoms; meaningful comparisons of CBT with other active treatments; identifying the populations and stages of psychosis where CBT may be most effective, adaptation of CBT in idiopathic cases; refining predictors of CBT outcome.

What Is CBT?

Although CBT is often styled a "talking therapy" [6], CBT has always been a multicomponent package involving a number of psychotherapy, behavioural, cognitive and non-specific processes.

CBT has been around since Beck [7] reported a treatment addressing reasoning for delusions in the 1950s. At this time with behaviourism as its heights, most treatments resorted to operant style programs to manage psychotic behaviour and verbalization. A key transition point noted by Alford and Beck [8] in the development of CBT for delusions was the distinction between modifications of

verbalizations, that is "verbal behaviour" and belief modification. Operant techniques had successfully modified delusional talk but had not addressed delusional thought. Thought stopping can successfully treat intrusive thoughts [9] and auditory and visual hallucinations [10]. But Marzillier and Birchwood [11] suggested cognitive rather than behaviour therapy was required to address delusional beliefs. Other major catalysts for the development of CBT were the introduction of cognitive models for depression and anxiety, the incomplete effects of medication and the appeal of Bellack [12] in his famous presidential APA address, where he termed schizophrenia "the neglected child of psychology". The medical brain disorder discourse dominated treatment throughout the 60s and 70s with experimental cognitive psychology paving the way to cognitive therapy through the study of information processing bias.

The goal of all CBT is to increase functioning and decrease distress. As Warman and Beck [13] point out, most existing CBT programs share common elements [14]. All approaches to CBT agree that the therapy must be conducted in an attitude of "collaborative empiricism". Firstly, there needs to be alliance and empathy and, for example, Chadwick et al. [15] suggest a preparatory period where a meaningful trustworthy and beneficial relationship is built up. Turkington et al. [16] summarize main techniques as developing a therapeutic alliance building based on the patient's perspective. This step involves using the patient's own terminology for their problem. Part of establishing collaboration is a non-confrontational approach. In other words, right from the start there is no attempt to label the person's belief as irrational or mistaken. Rather team work is emphasized with the aim of considering the delusion or hallucination as one hypothesis amongst several which can be tested collaboratively with the therapist. A very important part of repositioning the person to their symptoms is normalization where the aberrant experiences are recontextualized in a more dimensional and continual sense. This normalization might apply to the symptoms themselves or the context in which they are experienced. A person with malevolent delusions may come from a distrustful family environment where paranoia may be adaptive. Further, the existence of hallucinations and fixed beliefs is not always in itself abnormal. In addition, contextual factors that might produce bizarre thoughts can be explained. Stress, for example, can narrow our attention and produce odd somatic symptoms. Certain anomalous signals or coincidences may trigger temporary paranoia. People with schizophrenia spectrum symptoms are frequently judgemental of themselves and symptoms and how others perceive them and an important initial task may be to break through the negative meta-cognitions and self-stigma attached to experiencing anomalous phenomena. In fact beliefs a person holds about their experiences may themselves signal distress.

"Reality testing" and "behavioural experiments" are usually employed later in CBT where the person and therapist collaboratively test the reality of certain hypotheses. The techniques need to be employed with caution since the presence of confirmation bias may easily disrupt pure testing. For example, adopting an attitude of suspicion may lead to others looking at the person suspiciously, which could be interpreted as proof of the paranoia. Hence, psycho-education combined with role

playing exercises on how communication can be influenced by attentional or confirmation bias, form part of CBT. Belief in delusions can be modified sometimes through asking the person to adapt a third-person perspective as though discussing the plausibility of someone else's delusional belief. A case formulation approach would also examine the meaning the person ascribes to the delusion, either by downward arrow (e.g., if people are following you, this means what?) or by personal construct theory where the relevance of the delusion is evaluated along distinct personally relevant dimensions. Questioning the person about the development of the delusion beliefs and inference chaining in which the personalized meaning of a systematized delusion is explored may help the person gain insight into gaps and inconsistencies and incoherences in their stories.

Dickerson [6] notes techniques such as focusing and re-attribution where a focus on a voice's physical nature, content, sequence and triggers, and the beliefs the person has about voices leads to attempts to reformulate voices as self-generated. Bentall et al. [17] reported moderate success with this method and a reduced duration of hallucinations.

A number of other studies have also used coping strategy enhancement [1]. This involves education of people in coping strategy enhancements for specific symptoms. Such strategies involve problem solving, attention switching, self-statements, modifying sensory input, and physical activity, breathing and relaxation. Haddock et al. [18] found distraction to be effective in the short term. Morrison [19] has also emphasized the importance of coping strategies as a buffer to psychotic symptoms, in particular in the role of installing a new response set to aversive triggers.

CBT Tailored for Specific Biases and Deficits

There has been a marked increase in the study of cognitive biases in schizophrenia and the integration of biases with cognitive-behavioral interventions in the disorder. Patients with paranoid schizophrenia jump to conclusions, show attributional biases, share a bias against disconfirmatory evidence, are overconfident in errors, and display problems with theory of mind [20]. Many of these biases precede the psychotic episode and may represent cognitive traits. Building upon this literature, Moritz and Woodward [20] developed a metacognitive training program that aims to convey scientific knowledge on cognitive biases to patients and provides corrective experiences in an engaging and supportive manner. The authors claim the increasing application of understanding of cognitive processes in schizophrenia in clinical treatment.

Moritz and Woodward [20] give an excellent overview of how specific exercises may apply to each meta-cognitive bias. For example, self-serving biases and attributional external biases may be dealt with through psychoeducation on negative consequences of self-serving bias and the benefits of multiple over mono-causal attributions. Jumping to conclusions can be met with illustrations of how premature

decisions lead to errors and the benefits of cautious data gathering. Also ambiguous elements can be used to demonstrate the fallibility of first impressions. Bias against disconfirmatory evidence can be addressed through showing how people can be led up the garden path in a complex deduction through trusting only what fits with prejudiced view. The role of empathy and theory of mind can be regulated by exposure to facial cues which do not always seem to be expressing the emotions initially identified. The way in which memory errors can occur depending on interference and context are rehearsed and people taught to distinguish between fake and true memories through use of a vividness heuristic. Other exercises require the point of view of the protagonist to be considered in a correct solution. The effect of mood, especially negative mood, in fostering over generalization, personalization and selective abstraction are illustrated.

Beck and Rector [21] suggest that a series of deficits typical of schizophrenia (such as attention, memory and executive function) may lead to cognitive insufficiency resulting in inferior performance and susceptibility to stress. The stress and emotional reactivity itself may lead increases in corticosteroids increasing likelihood of delusions and hallucinations. They propose that many apparent failings may result from deficits, such as difficulty in self-monitoring, impaired insight, reality testing, self-centred focus, externalizing, categorical thinking, emotion and somatic-based reasoning. Low pre-morbid expectations may lead to the perception of limited resources, social isolation, anticipated personal slights. Consequently the clients may need to be coached in basic skills. They propose educating clients through stress vulnerability and positive coping and dealing with negative symptoms at the same time as positive symptoms rather than leaving the negative to be dealt with as a consequence of the positive symptoms. They suggest techniques such as behavioural monitoring, activity scheduling, mastery and pleasure ratings.

Meta-Cognitive Approaches

A series of studies have emphasized the importance of meta-cognition not only to overcome symptoms but to enhance quality of life and function. Davis and Lysaker [22] identified two types of meta-cognitive beliefs which might affect rehabilitation, firstly, beliefs about failure and stigmatization as ill, secondly ideas about danger and insecurity in the environment. These authors suggest meta-cognition involves a set of semi-independent abilities including self-reflectivity, and understanding the others' mind. In a single case study, the authors showed that dealing with meta-cognitive appraisals under four modules: "thinking about work", "barriers to work", "work place relations" and "realistic self-appraisals", reduced dysfunctional meta-beliefs by about 20% and could form a useful adjunct to CBT. The meta-cognitive therapy also helped access emotions and core beliefs and understanding the other's mind. Dimaggio and Lysaker [23] recently reviewed developments in assessment and application of metacognitive disturbances in schizophrenia.

Group vs Individual Therapy

Group approaches have been found useful in CBT for a number of psychiatric disorders and some studies have demonstrated they could prove useful in schizophrenia. Clinically, individuals with schizophrenia often feel isolated and a group setting can offer normalization, opportunities for socialization, as well as the chance to exchange experiences, perceptions and coping strategies. Studies using the group format include Wykes' group for voice hearers seeing improvements in self-esteem and in negative experiences of voices [24], Granholm et al. [25] integrating skills training to CBT for psychosis with older individuals with schizophrenia showing improvements in negative symptoms and social functioning, Landa et al. [26] focusing on paranoid delusions with preliminary results being quite promising, with moderate decreases in the character of the delusions.

Lecomte et al. [27], comparing group CBT for psychosis to another evidence-based intervention (social skills training for symptom management) for individuals in early psychosis, found greater advantage for the CBT approach compared to the skills training approach, mainly in improvements on psychosocial variables such as self-esteem, coping strategies and social support. Both interventions proved efficacious in decreasing positive, negative and overall symptoms compared to the control group. The same team also obtained positive results using CBT techniques group formats to increase self-esteem of individuals with more chronic schizophrenia [28, 29] and to improve stress management [30].

Adapting CBT to Poor Insight

CBT may require adaptation for people with poor insight, alcohol abuse, and cognitive impairment [19]. Useful techniques where there is lack of insight include: reducing stress, empowering control over behaviour, tracking constructive experiences and activity level, treating the voices as noise and not letting them interfere. Perivoliotis et al. [31] illustrate CBT in a case with lack of insight. The voices and delusions were not directly addressed and rather therapy hinged on trying to get the patient back to work and functional despite the voices. Pervoliotis et al. [31] reported a softening of convictions and growing mental flexibility after 66 sessions.

Adapting CBT to Poor Compliance

Rector [32] has emphasized the crucial role of homework compliance in CBT, noting that consolidating feedback from homework assignments is essential to improve between session functioning. Mostly feedback includes a close monitoring of the different stages in treatment. Several factors can limit homework compliance, including low motivation, reducing effort, trouble initiating goal-directed activities,

plus beliefs about performance. Rector [32] suggests implementing an assignment and a review stage to monitor the monitoring, as well as taking account of cognitive problems such as poor attention, organization and memory. Rector [32] also emphasizes being flexible in approaching appraisals or content and behavioural or cognitive aspects in therapy, depending on the impact of each component.

Does CBT Work Equally with All Symptoms?

Tarrier et al. [33] investigated whether different types of psychotic symptoms are more or less responsive to CBT compared to treatment received by control groups. Seventy-two patients suffering from chronic schizophrenia who experienced persistent positive psychotic symptoms were assessed at baseline and randomized to either CBT and routine care, supportive counselling and routine care, or routine care alone and were reassessed after 3 months of treatment (post-treatment). Independent and blind assessment of outcome indicated delusions significantly improved with both CBT and supportive counselling compared to routine care. Hallucinations significantly decreased with CBT compared to supportive counselling. There was no difference in the percentage change of hallucinations compared to delusions in patients treated by CBT. There was little change in measures of affective symptoms but there was no evidence that a reduction in positive symptoms was associated with an increase in depression. In fact, a reduction in positive symptoms was positively correlated with a reduction in depression. There were significant differences in the reductions in thought disorder and negative symptoms with an advantage of CBT compared to routine care.

Use of CBT in Different Stages of Psychosis

CBT for psychosis does not appear to show the same results according to when it is offered. Valmaggia et al. [34] adapted CBT across the three stages of psychosis: prodromal, first episode and chronic. They suggest that in the prodromal case, therapy should be directed to "at risk" situations, in particular ones likely to lead to social isolation and intensification of triggers for anxiety and self-appearance. As such, Morrison et al. [35] conducted a large trial, involving randomizing individuals who were considered at risk of developing psychosis to receive individual CBT (focusing on issues or goals mentioned by the individual, not specifically linked to psychosis) or treatment as usual (i.e. being followed). They found significant advantages to receiving CBT, namely a reduced rate of developing psychosis in the years to come compared to the control group. In the first episode case, CBT was applied to positive symptoms, to emotional and social adjustment, and to refining coping strategies, in particular self-judgements and behavioural activation. Drury et al. [36] were the first to apply CBT to recovery of an acute episode (not solely first episodes) compared to a recreational activities support group. Both groups improved but the CBT showed

better "control over illness" perceptions. Of the large trials investigating using CBT for individuals with a first episode of psychosis, such as the SoCRATES trial [37], the COPE trial [38] or Lecomte et al.'s [27] trial, only the latter obtained significant and important results. This finding has led Saksa et al. [39] to suggest that perhaps CBT finding for psychosis is more effective in group formats for individuals in the early stages of the illness, whereas older or more seasoned patients really do benefit from the individual format. CBT for refractory symptoms have by far been the most studied and have demonstrated important impact on various indexes of well-being, including decreased positive symptoms and better quality of life. Again, the focus is not solely on the psychosis since other problems, such as being alienated from family and friends, social anxiety, depression or past traumas, can also become treatment targets.

French et al. [40] detail three cases representing potential routes into the development of psychosis. The authors highlight the fact that this high-risk group is not homogenous in terms of specific symptomatology. All three cases indicate the importance of engagement and some of the difficulties in this process. However, once engaged the clients collaborated effectively in the process of treatment. The model described directs treatment strongly towards metacognitive beliefs, selective attention strategies, and the manipulation of safety behaviours. Significantly, in the one case that went on to develop psychosis there was a strong positive belief about the psychotic symptoms in the early stages, which again has implications for future treatment protocols. This is supported by evidence from Morrison et al. [41] who found that positive beliefs about unusual perceptual experiences were the best predictor of predisposition to hallucinations in normal subjects, whilst negative beliefs about hallucinations may be associated with unhelpful coping strategies. Therefore, negative beliefs regarding the appraisal of the voice as being dangerous or uncontrollable may signal a transition to psychosis. These factors need further research and may help in developing specific cognitive interventions to treat this group of ultra high-risk clients.

The most studied CBT for psychosis approaches have been in regards to chronic persistent symptoms [18]. Small controlled trials have indicated that cognitive-behavioral treatments can significantly reduce positive symptoms in the short term [1, 17, 42]. Further evidence has emerged from three large well-controlled clinical trials recently conducted in the United Kingdom. CBT with routine care have been shown to be superior to routine care alone, consisting of maintenance medication and case management, at post-treatment and at 9 months [43, 44]. A second trial demonstrated cognitive therapy to be superior to befriending control at 9-month follow-up, although there were no differences at post-treatment [45]. The third trial [2] compared intensive CBT and routine care with supportive counselling and routine care with routine care alone. At post-treatment, patients who received CBT showed significant improvements in psychotic symptoms compared with routine care alone; those receiving supportive counselling being in an intermediary position [46]. At the 1-year follow-up, differences between CBT and supportive counselling had narrowed, but patients who received either of these treatments showed significantly less positive and negative symptoms than the routine care-only group [2].

Medication and CBT

The majority of controlled CBT trials have included people on medication; in some cases 100% of cases are receiving effective doses of neuroleptics, mostly new generation. In general, there seems no contraindication to administering CBT together with medication. CBT has shown extra benefits in drug-resistant cases [42], and CBT has been employed to help adherence to medication through offering complementary non-medical models [16]. However, frequently in controlled studies the type of medication was not standardized or controlled with a mix of first and second generation antipsychotics. Rector et al. [47] reported no differences in outcome between these participants receiving or not receiving medication or between different dosage levels.

Evaluating CBT Gains

As noted, not all CBT for psychosis is delivered uniformly. There are two major schools in the UK formulation using a manual-based delivery, whilst the US studies are a mix of skills training with CBT. Early trials [36] generally involved an initial preparation stage, followed by challenge of beliefs in a supportive environment. Current CBT for schizophrenia includes psychoeducation about the nature of psychosis in order to reduce self-directed stigma and normalize these experiences; strategies to reduce the subjective distress associated with the disorder; specific cognitive and behavioral strategies to reduce the occurrence and distress associated with delusions and hallucinations; and strategies to reduce comorbid anxiety and depression. CBT produces large clinical effects on both the number and severity of positive symptoms, especially the distress associated with delusions and hallucinations, as well as general psychopathology at treatment end-point and in follow-up [48, see review].

Tarrier et al. [33] compared intensive CBT with routine care and supportive counselling plus routine care. In Tarrier et al.'s [33] study *intensive CBT plus routine care* had three components: (a) coping strategy enhancement aimed to teach patient specific methods of coping with their symptoms and aimed to reduce positive symptoms, (b) problem-solving training, and (c) relapse-prevention strategies to reduce future relapse risk. Each component consisted of 6 hourly sessions each, plus two final summary sessions. Twenty sessions of treatment were conducted twice weekly over 10 weeks. After post-treatment assessment, four booster sessions were given, one a month for 4 months. *Supportive counselling plus routine care* aimed to provide emotional support through the development of a supportive relationship fostering rapport, unconditional regard for the patient, and social interaction. General counselling skills were used to maximize the non-specific effects of intervention. The therapist maintained an interest in the patient and discussed with him or her problematic issues, although not symptoms, and through reflective listening attempted to build a supportive relationship with the patient. Therapy was unstructured and followed the lead given by the patient. Supportive counselling followed an identical format to the CBT intervention (20 sessions with four booster sessions after

post-treatment assessment). Hallucinations and delusions reduced more in CBT with a small effect size but supportive counselling showed some improvement. The CBT improved symptoms regardless of thought disorder and also modified negative symptoms.

There is still some debate over the "equivalence paradox" with apparently non-specific treatments such as relaxation and stress management and supportive counselling, showing better than expected effects [49]. Tarrier et al. [33] point out that supportive counselling may help in delusions since one dimension of delusions is feeling understood but is not helpful in hallucinations and other symptoms. Furthermore, trial methodology in these early trials was not strong, with bias in allocation and attrition.

Gould et al. [50], in an attempt to find a common metric to the "apples and oranges" of CBT, calculated effect size across studies, which had used a control group. Of 25 studies initially screened, only 7 met criteria of focusing on change of psychotic symptoms. CBT treatment duration was between 5 and 20 week sessions. The studies were representative of schizophrenia spectrum disorders, with 89% diagnosed as schizophrenia, 7% with schizo-affective disorder and 4% with delusional disorder, and 100% on medication. Effect size across studies was calculated using the Smith and Glass algorithm. Most studies were individual treatment sessions carried out by doctoral level clinicians. Effect sizes varied between 0.20 and 1.26. The mean effect size across studies was 0.65 but in all studies, improvement increased at 6-month follow-up to a 0.93 effect size. Most studies did not look at longer term functioning issues including rehospitalization. Also the closer the control condition was to active matched treatment, the smaller the effect size.

The meta-analysis of Gould et al. [50] was criticized by Zimmermann et al. [51] for not taking account of sample size and for excluding certain randomized studies. Zimmermann et al. (2005) focused on change in positive symptoms, using a more sophisticated measure of effect size. Zimmermann et al.'s [51] review provides effect size analyses for controlled studies of cognitive behavioral treatments of positive symptoms in schizophrenia spectrum disorders published during the last 15 years.

This meta-analysis, using a sample of 14 outcome published studies, supports the general conclusion that CBT is a promising approach for adjunctive treatment of positive symptoms in patients with schizophrenia. Moreover, in this meta-analysis the therapeutic effects are preserved at follow-up, suggesting that the CBT has long-term effects [52]. The global mean weighted effect size of 0.37 is considered as modest, which is not surprising, according to Tarrier and Wykes [5], given the severity of the disorder. This effect size dropped even to 0.29 when only blinded trials were considered, and was significantly lower than the effect size reported in the study of Rector and Beck [48]. Furthermore, the results showed that CBT has a better effect on patients in an acute psychotic episode (mean weighted effect size = 0.57) than on stabilized chronic patients suffering from persistent psychotic symptoms (mean weighted effect size = 0.27). The comparison groups designed to control for non-specific effects of therapy differ greatly between studies, ranging

from waiting-list [1, 42] to manual-based and supervised supportive counselling [46, 53, 54]. Further effect sizes analyses indicate, as expected, that CBT is more superior to waiting-list than to non-specific intervention (mostly defined as supportive therapy) and treatment as usual. Interestingly, as noted, the effects of CBT are slightly less pronounced when it is compared with treatment as usual rather than with non-specific treatment, such as supportive counselling. O'Connor [55] showed only moderate effect sizes in delusional disorder when comparing CBT to an active listening placebo condition.

Pilling et al.'s [56] demonstrated that CBT was effective in improving mental state, both during treatment and at follow-up. On continuous measures, this effect was only visible at follow-up. The authors conclude that the finding of a positive impact of CBT on mental state is not surprising, as CBT tackles the underlying cognitions hypothesized to be inextricably linked to mental state. But why positive effects on continuous measures of mental state are only apparent at follow-up is less clear. Likewise Wykes et al.'s [57] meta-analyses supported the benefit of CBT, showing moderate effect sizes (0.40) but pointed to the heterogeneity of methodological rigour. There was a significant relationship between poor trial quality as measured by clinical trial assessment measure and effect size and unmasked assessment inflated effect sizes.

In Jackson et al.'s [58] study, a CBT intervention known as Active Cognitive Therapy for Early Psychosis (ACE) was compared with befriending over 20 sessions of therapy. ACE significantly outperformed befriending at mid-treatment assessment but there were no differences between treatments in positive or negative symptoms or hospital readmissions at 1-year follow-up. Gaudiano [59], reviewing 12 controlled clinical trials of CBT, estimated that 42% of CBT conditions compared with 25% of comparison conditions demonstrated reliable change.

CBT for Negative Symptoms

Recent work has also tailored CBT to negative symptoms. The management of negative symptoms is especially important as these represent the most debilitating aspect of schizophrenia and predict an overall poor prognosis [60]. It may be that some negative symptoms reflect cognitive, emotional, and behavioral dysfunction rather than stable deficits and are therefore amenable to change via strategies that have proven effective in harnessing motivation and social and emotional reengagement in those with severe emotional disorders. Early work had viewed negative symptoms as due to skill deficits. Other approaches viewed negative symptoms as retreat in the face of extreme stress [61]. CBT was adapted from depression to deal with anhedonia, amotivation is addressed through mastery pleasure activation.

Perivoliotis and Cather [62] review a cognitive model which views negative symptoms as a maladaptive strategy to protect from pain and rejection of engagement. They identify a number of beliefs about performance, resources, social acceptation, stigma, low expectations. They report a case study showing mild

improvement. Some authors have argued that loss of delusions could lead to a loss of meaning in life and to consequent increased depression.

Research is now required to test the efficacy of CBT for negative symptoms in patients with primary negative symptoms and the comparative absence of positive symptoms, to provide a direct examination of its potential for reducing these debilitating symptoms independent of associated symptom domains (i.e., positive symptoms). Anxiety is frequently comorbid in psychosis and needs to be addressed separately as a component of distress.

Predictors of Outcome

Prouteau et al. [64], in a prospective study in patients participating in a rehabilitation program, showed that worse baseline sustained attention predicted better self-rated quality of life, and that better baseline associative visual memory predicted better community functioning over the rehabilitation follow-up period, in particular, higher autonomy in activities of daily living, and less physical and psychiatric symptoms that could interfere with rehabilitation. Baseline cognitive performances also predicted community functioning improvement between baseline and follow-up assessments: associative visual memory predicted improvement in daily living autonomy and in social competence; sustained attention predicted improvement in behavioral problems (such as medication compliance, collaboration with treatment providers or impulse control) and social competence; and planning performances predicted improvement in daily living autonomy.

The lack of symptomatic assessment did not permit the authors to explore a possible confounding effect of symptomatology on the reported associations. The authors' results suggest that each dimension of psychosocial functioning requires specific cognitive abilities. The finding that associative visual memory predicts long term autonomy in activities of daily living is in accordance with that obtained by Velligan et al. [65] in a longitudinal study conducted in outpatients with schizophrenia attending usual ambulatory care, showing that visual memory was the main cognitive predictor of activities of daily living at 1.5 years. A paradoxical finding was that lower sustained attention predicted better long term self-rated quality of life. Despite apparent contradiction with above results, this finding might be explained by different relationships between cognition and objective versus subjective outcomes [66, 67].

McGowan et al. [68] reported a qualitative study showing that ability to let go of beliefs, logical thought and presence of a shared goal were valid predictors of outcome. Haddock et al. [69] reported that older people engaged more in CBT than younger people. Intellectual disability may not necessarily be a contraindication to treatment [70]. Garety et al. [71] reported that cognitive flexibility, which was correlated with insight, predicted benefit from CBT, while a brief test of cognitive impairment did not. A recent study by Beauchamp et al. [72] showed that personality profiles specifically linked to the ability to develop new coping strategies predicted

group therapy outcome in early psychosis. Schizotypy may be an underlying vulnerability factor for both unacceptable intrusions and unusual or bizarre experiences [63].

Further research is needed in larger samples to determine whether reliable predictors of treatment response can be identified.

Additions to CBT

Brent [73] has identified an impairment in mentalization as a focus for therapy in psychosis. The rationale is that the development of mentalization or thinking about interactions as motivated by mental states is deficient in psychosis. This development relies on secure attachment where the core giver validates the child's inner senses, so providing a basis in later life for the person to understand other's mental states. The aim of mentalization based psychotherapy is to re-establish an attachment relation. The therapist provides empathic reflection on the patient's current mental state and affective experience using the therapists mind as a model. There was improvement in one case study.

Serruya and Grant [74] suggested the use of mental imagery as a way of addressing the development and maintenance of anxiety in psychosis. Mental imagery refers to perceptual information from memory and imagination rather than sense organs. Images occur in 74% of psychosis. Morrison [19] described a case study where rescripting (changing end point of the image) promoted a sense of control. Imagery was used more in terms of imaginal exposure as an adjunct to CBT. An important precedent here was triggering psychosis during a therapy session through imagery.

Johnson et al. [75] report use of loving-kindness meditation, a type of concentration meditation focused on directly warm compassionate feelings. Results were positive in a non-clinical sample, indicating improved anticipatory pleasure, social connectedness and environmental mastery. Three case studies were promising and included mindfulness training. Therapies including music therapy, vocational, animal assisted, activity-based therapy have shown benefits.

Family counselling can also be a beneficial addition to CBT. In the Pilling et al.'s [76] meta-analysis, all family interventions (i.e. both single and group family therapies) were more effective at reducing relapse in the first 12 months of treatment. The largest effect was obtained in trials comparing family interventions with standard care. Family treatments are effective at reducing readmission, with the greatest effect being apparent for single family treatments. All family interventions had lower rates of treatment non-compliance than comparison active treatments, and all increased compliance with medication in comparison to all other treatments. It was not possible to identify any particular family characteristics (e.g. levels of expressed emotion) or patient characteristics (e.g. severity of disorder or age of onset) associated with different outcomes. Neither did clear evidence emerge of an impact of the frequency or duration of treatment on outcomes.

Some attempts have been made to integrate neurocognitive and cognitive remedial findings with cognitive therapy. Deficit in social cognition, in particular theory of mind, has been linked with schizophrenia onset. Chung et al. [77] reported that theory of mind was characteristic of prodromal schizophrenia but may be mediated by IQ and may be particularly important for set shifting during therapy.

Combs et al. [78] addressed social cognition deficit in therapy. They suggested that social cognition may have a greater impact on outcome and functioning than neurocognition. However, according to Combs et al. [78], previous studies have been too specific in addressing single abilities like emotion, perception and theory of mind. To address these limitations, Combs et al. [78] developed Social Cognition and Interaction Training (SCIT; Roberts DL, Penn DL, Combs, DR, 2006 Social cognition and interaction training manual, "unpublished manuscript"). SCIT is a flexible 18–24 week, group based, manualized intervention designed to improve emotion perception, attributional style, and theory of mind abilities for persons with schizophrenia. Also, SCIT participants showed improvement in cognitive flexibility, need for closure, and self-reported social relationships and a significant reduction in the number of aggressive behaviours on the treatment unit. These improvements were found even after controlling for changes in psychiatric symptoms over time. The authors report that individuals who participated in SCIT showed improved social cognition, social relationships, cognitive flexibility, and reduced aggression.

Social and cognitive skill training has been controversial. Pilling et al.'s [76] Cochrane review considered the many controlled trials and systematic reviews of social skills training claim positive results and concluded in a meta-analytic review of randomized control trials that the evidence was unconvincing with few observed benefits of social skills training in a range of settings. Accordingly, Pilling et al. [76] did not recommend the use of social skills training in routine clinical practice. The position with regard to cognitive remediation was also disappointing. Pilling et al. [76], reviewing a small series of recent randomized controlled trials, provided no consistent evidence of appreciable positive effects of cognitive remediation. However, the review may have been over-critical and efforts are still directed to moulding psychological and environmental interventions that take account of the cognitive deficits present in schizophrenia and focus therapeutic efforts on the improvement of functional deficits. Other additions to CBT repertoire include motivational interviewing [79]. Preliminary studies have indicated that acceptance and commitment therapy [80] and compassionate mind training [81] may form useful adjuncts.

Conclusions and Further Questions

Cognitive techniques employed within CBT can be divided into those adapted from CBT approaches to anxiety and depression, those designed specifically to address biases typical of schizophrenic spectrum symptoms, and more general

coping techniques or stress management. There is a shift away from linear formulations of irrational thinking leading to maladaptive emotions, thoughts and behaviours to viewing these factors as perhaps independent reflections of a way the person relates to the world. This has led to looking at the way people regulate thoughts and emotions, attempt to react and control thoughts and feelings and overall patterns of attachment and relating. Mindful approaches indicate that attempting non-judgemental acceptance of voices might help adaptation. Recent emphasis has been placed on changing the maladaptive way people ordinarily cope with their symptoms often unsuccessfully, and react and try to change them. Instead, the aim is to encourage compassionate mind training and help people through self-care to become aware, sensitive and respectful of their own needs. Highlighting personal goals, either through a method of levels or traditional goal orientation and problem solving is also helpful, as is placing priorities in order to relativize the impact of symptoms. Such approaches could even encourage viewing symptoms as benefits or resources and making them central to the person's strengths [80].

Recent CBT models agree on the necessity to address the context surrounding the symptoms and what tends to give them significance, and in particular behaviours stemming form the initial reaction which effectively maintain the vicious circle of negative and positive symptoms. Figure 12.1 illustrates how such a vicious circle is maintained in the case of distress from auditory hallucinations and delusions. Kuipers et al. [82] have recently placed stress vulnerability and stress management as a key component in understanding symptomatology.

Tarrier and Wykes [5] note the following points to consider in future CBT outcome studies: variability in therapist alliance and competence and the lack of research on this factor; several sources of variability in clinical trials are under controlled; poor quality of allocation may account for 30–40% exaggerated estimates; sample recruitments have not always been random or representative and may too often be "best bets". Often time requirements on the health system restrict selection only to amenable patients. Also some trials are under powered and the clients are over-worked and fatigued in completing experimental demands and questionnaires. Control treatments-as-usual are no longer admissible as they are, in any case, constantly developing and include multiple confounds. CBT evaluations and treatments should be uniform or at least replicable across studies and could follow use of Clinical Trials Assessment Measure.

Another point concerns how CBT validated in clinical trials should be rolled out into practice. Spidel et al. [85, 86] have discussed, at length, issues in the implementation of CBT in community settings. Amongst the challenges noted are: transport costs, suitable locations, engaging and motivating clients, attitude of organizations and clinicians, competing groups or activities. These authors encourage the use of manuals, training workshops and other constructive benefits to encourage collaboration. Others have tried to improve implementation by informing parent groups of the benefits of CBT for psychosis, who in turn put pressure on the clinics and government for it to be offered more widely.

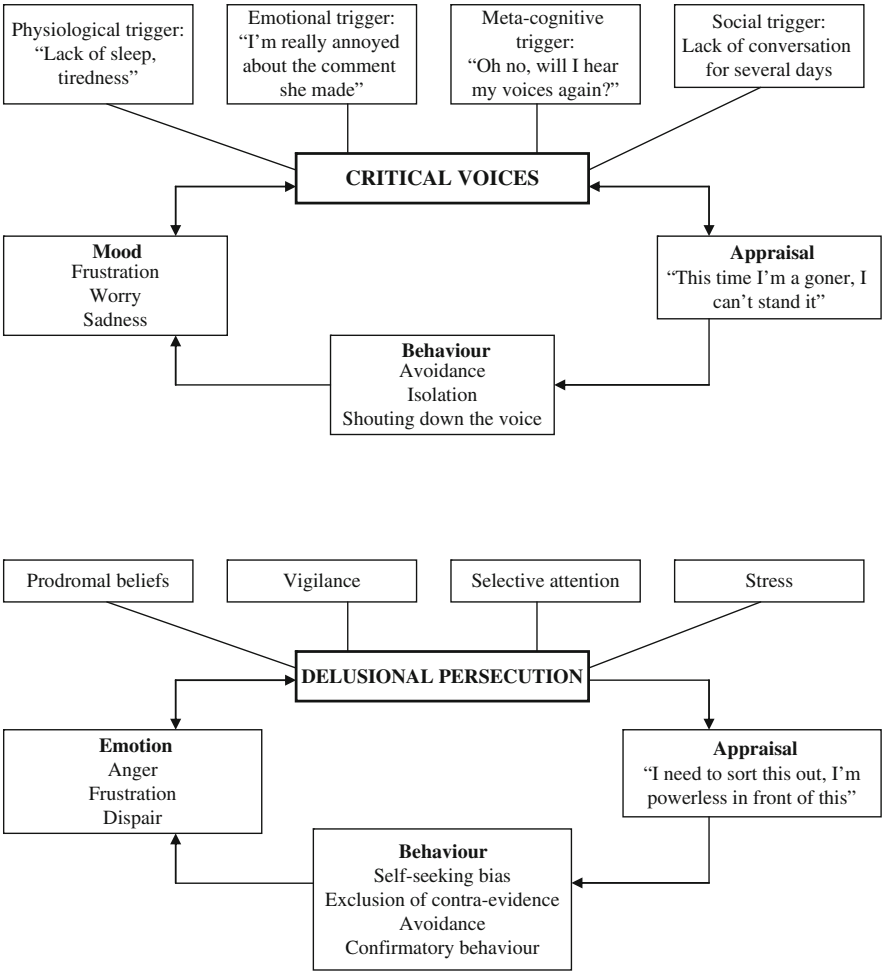

Fig. 12.1 CBT model of triggering and maintaining factors of two schizophrenic spectrum symptoms. Adapted from Garety et al. [83] and Tai and Turkington [84, figure 1]

An important issue concerns which components of CBT are effective active ingredients. There seems no standard CBT delivery package and there are clearly overlaps with other psychotherapies [87]. Many essential ingredients described in Morrison and Barratt's [14] Delphi study can be found in other therapies, whereas other approaches are more specific and stress the importance of homework or case formulation. There are however many patient, therapist and process variables to be considered in studies to come. Other parameters of treatment delivery to standardize include the duration of therapy which varies across studies between 5 and 60 sessions and length of acceptable follow-up (3, 6 months; 1, 2 years).

Finally, there is the question of who can administer CBT. Bradshaw and Roseborough [88] suggest therapists should receive training in CBT for schizophrenia and possess a fundamental comprehension of CBT and experience with CBT in clients without psychosis [16]. However, as Lecomte et al. [27], and Durham et al. [89], Bradshaw and Roseboroughs' [88] study, and Turkington et al. [90] have demonstrated, it is possible for non-psychologist mental health staff to be efficiently trained to conduct CBT for psychosis and obtain significant clinical results – therefore increasing the number of people able to offer CBT. In Bradshaw and Roseboroughs' [88] study, the therapists were licensed clinical social workers who had master's degrees in social work and an average of 5 years in mental health experience. The therapists received 48 h of training in CBT over a 6-month period. Training also involved administering CBT to three clients under clinical supervision. Lecomte et al.'s study [27] involved mental health workers (psychiatric nurses, psychiatrists, social workers, occupational therapists, psychologists, and counsellors) from early intervention in psychosis clinics who received a 2-day intensive workshop along with a semi-structured manual and weekly supervision. The psychiatric nurses, trained to provide CBT in Turkington et al.'s [91] study, received an average of 10 days or training and participate in supervision on a weekly basis. Turkington et al. [91] also trained counsellors (who have previously treated schizophrenia) to learn the fundamentals of CBT for schizophrenia, with 2 weeks of rigorous training and continual supervision by a CBT expert [90]. Treatment guidelines [4, 92] provide practical resources for the application and status of CBT for schizophrenia. The availability of CBT for clients with schizophrenia is dependent on the accessibility of supervision and administrative support [16]. All factors considered, given the empirical support for CBT for schizophrenia, integrating CBT into diverse clinical professional repertoire seems optimal.

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Chapter 13
Schizophrenia and Medical Illness: Is Medical Illness the Consequence of Schizophrenia or Its Treatment?

Jimmi Nielsen

Abstract Patients with schizophrenia have a lifespan that is more than 20 years less than that of the general population. It has been suggested that treatment with antipsychotics is a reason for their reduced lifespan, but patients with schizophrenia are also known to have a more sedentary and unhealthy lifestyle, including heavy smoking, inactivity and obesity. Some antipsychotic medications increase the risk of diabetes and dyslipidemia, but, on the other hand, suboptimal treatment increases the risk not only of suicide but also violent behaviour. Furthermore, it is known that patients with schizophrenia are less likely to seek medical help for their somatic diseases. This chapter discusses medical illnesses associated with schizophrenia and its treatment with focus on monitoring and intervention in order to reduce mortality.

Keywords Metabolic syndrome · Antipsychotic · Schizophrenia · Diabetes · Extrapyramidal side-effects

Abbreviations

BMI	Body mass index
CATIE	Clinical antipsychotic trials of intervention effectiveness
DVT	Deep venous thrombosis
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EPS	Extrapyramidal side-effects
HIV	Human immunodeficiency virus
MR	Magnetic resonance
OR	Odds ratio
RR	Rate ratio
SD	Standard deviation
SMR	The standardized mortality ratio
TdP	Torsades de pointes

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Introduction

Patients with schizophrenia have a reduced lifespan of more than 20 years, with cardiovascular disorders being the main cause of death [1–3]. The somatic well-being of patients with schizophrenia has been neglected for decades [4] despite a somatic co-morbidity rate as high as 74% [5]. Several factors contribute to increased mortality, e.g. a sedentary lifestyle, less motivation for improving their physical condition, etc. Moreover, patients with schizophrenia are not always offered proper, timely somatic treatment, e.g. because they interpret physical symptoms in a way that does not prompt them to seek medical assistance, as when chest pains are interpreted as radiation from the TV. Even though patients with schizophrenia may recognize physical symptoms, they may be afraid of going to their general practitioner because previous visits have led to involuntarily hospital admission. Furthermore, physicians are less skilled in communicating with patients with schizophrenia, thereby reducing the likelihood of detecting physical symptoms. Psychiatrists, on the other hand, may be less well trained in diagnosing somatic disease, and this could also lead to perilous situations. This chapter describes and discusses the increased somatic morbidity and mortality of patients with schizophrenia in the context of the disease as well as its pharmacological treatment. For more information about the types of pharmacological treatment, please read the relevant chapters in this book. As it is beyond the scope of this chapter to cover all somatic diseases occurring in patients with schizophrenia, the diseases covered in this chapter are only examples.

Overall Mortality

Patients with schizophrenia have an increased risk of premature death and their lifespan is shortened by approximately 20 years [3] compared to the general population. As early as the first half of the twentieth century, a 2–4 times increased mortality rate was found in patients with schizophrenia [6]. Overall mortality is best illustrated by using the standardized mortality ratio (SMR), which is the mortality in a specific population compared to the mortality in the background population matched by age and sex. Thus an SMR of 2 means a double risk in patients with schizophrenia compared to the background population [3]. An SMR can be calculated for overall mortality or for specific causes, such as cardiovascular disease. A systematic review of 37 articles from 25 different countries found the following SMR for patients with schizophrenia [3]: overall 2.58, suicide 12.86 and cardiovascular 1.79. Suicide is a relatively rare cause of death in the general population which explains the high SMR for suicide. A study by Brown found that 12% of the reported deaths for this patient group were suicides, which accounts for 28% of the excess mortality [6]. This means that even when death from suicide is excluded, there is still a substantial increased mortality.

Another interesting finding from the study by Saha et al. [3] was that the gap between patients with schizophrenia and the general population regarding overall mortality has increased in the course of the last few decades. Median SMRs for

overall mortality for the 1970s, 1980s and 1990s were 1.84, 2.98 and 3.20, respectively [3]. In the same period new methods for reducing cardiovascular mortality were developed and implemented, resulting in the decreased overall mortality in the general population. While the general population has benefitted from these new interventions, patients with schizophrenia have done so to a lesser degree because the overall mortality rate in the general population has decreased more rapidly than in patients with schizophrenia, thereby creating an increasing mortality gap. A further concern is the extensive weight gain properties of the atypical antipsychotics introduced in the mid-90s [7]. However, atypical antipsychotics are a heterogeneous class of drugs with regard to their weight-affecting potential, with clozapine and olanzapine causing most weight gain and ziprasidone and aripiprazole causing least. The potential of antipsychotic drugs to induce weight gain is often underestimated because data on weight gain often come from short-term studies involving chronic patients already undergoing treatment with antipsychotics, i.e. patients who have already gained weight as a result of taking the antipsychotic under study. Nevertheless, Kahn and his co-workers [7] found a mean weight gain for olanzapine, the most widely used atypical antipsychotic, of 13.9 kg during a 12-month study in first-episode schizophrenia patients. Also ziprasidone, an antipsychotic drug otherwise considered to be weight-neutral, was associated with a 4.4 kg weight gain. As olanzapine was not introduced before 1996, we have yet to see the full effect of the weight gain induced by this extensively used antipsychotic on the mortality rate for schizophrenia.

Not all physical diseases, however, have a higher occurrence in patients with schizophrenia; the illness is thus associated with a decreased risk of rheumatoid arthritis [8, 9]. Cancer also seems to be less frequent (see later in this chapter). Nevertheless, we must conclude that patients with schizophrenia have a substantially increased overall rate of mortality.

Lifestyle of Patients with Schizophrenia

Schizophrenia is a chronic and often progressive disease. Approximately 10% of the patient population live in an institution [10], and lead more sedentary lives. One study found that patients with schizophrenia were less likely to do strenuous exercise [11], which could be due to their unemployed status [12], early retirement, difficulty in engaging in relationships with other people, etc., all of which makes it more difficult to maintain a sports training programme or to exercise. Besides, the average schizophrenia patient eats more fast food and a larger part of their diets consists of calories from high-fat and high-carbohydrate sources [11]. A study has established that patients with schizophrenia are less likely to consume fruit, milk and potatoes and that their consumption of vegetables is less than half of the amount recommended [13]. Furthermore, negative symptoms such as the lack of motivation and reduced energy levels may contribute to the difficulties of maintaining an active and healthy life style.

Smoking is a risk factor for respiratory and ischemic heart diseases and makes a significant contribution to the increased mortality [14]. The prevalence rate for

smoking in patients with schizophrenia has been found to be as high as 88% [15]; about three times that of the background population. Impaired nicotinic neurotransmission has been suggested as a reason for the increased prevalence of smoking in patients with schizophrenia. The increased prevalence of smoking is found to be present before the onset of psychosis [16]. Furthermore, studies show that not only do patients with schizophrenia smoke more [11], they are also more efficient smokers, whose habits result in the extraction of more nicotine from smoking cigarettes [17]. In conclusion, the use of tobacco in patients with schizophrenia remains a significant risk factor, adding to the increased mortality found within this patient group.

The sedentary lifestyle does not seem to be a consequence of the treatment or the course of the illness. A study thus found that the sedentary lifestyle was already present before the first episode of schizophrenia occurred [18].

Patients with schizophrenia often have a lifestyle involving a greater number of risk factors such as the abuse of substances or alcohol. After tobacco, alcohol is the most prevalent substance abused (20–60%), followed by cannabis (12–42%), cocaine (2–25%) [19] and amphetamines (2–25%) [20]. The occurrence of HIV among schizophrenia patients is not entirely elucidated, but a study has suggested a 3.1% prevalence, which is eight times the rate in the US background population [21]. The increased risk in patients with schizophrenia is probably due to a higher use of injecting drugs, trading sex for money or poorer knowledge of HIV-risk behaviour [22].

Even though the burden of a sedentary lifestyle seems to be the more important factor, medical intervention can still make a difference. In a study by Wu and co-workers, it was found that lifestyle interventions were effective in reducing antipsychotic-induced weight gains and that they worked even better when combined with metformin treatment of patients with first-episode schizophrenia [23]. The placebo group showed an average body weight gain of 3.1 kg whereas the lifestyle intervention group achieved a 3.2 kg weight loss during the 12-week intervention period. The group that received metformin in combination with lifestyle interventions achieved a significantly higher weight loss (4.7 kg) in comparison to patients undergoing only a lifestyle intervention. These data support the importance of monitoring patients with schizophrenia and are a clear indication that psychiatrists should focus more on ensuring proper health monitoring of this vulnerable patient group and on providing the necessary care and interventions.

Access to Somatic Treatment

Patients with schizophrenia are less inclined to undergo routine health checks and less likely to seek treatment for somatic illness. One study found lower likelihood of patients with schizophrenia to visit their general practitioner [24] to have their blood pressure and cholesterol level checked [25]. Several causes have been cited for this: 1) Altered pain sensitivity [26]; an older study has suggested a higher rate of silent acute myocardial infarction [27]. 2) Physical symptoms are interpreted in terms of a delusion or as the result of other psychotic symptoms, e.g. when chest pain from

acute myocardial infarction is interpreted as the result of radiation from outer space or patients think the symptoms is the results of the medication and therefore leading them to discontinue the medication. 3) Negative symptoms inhibit patients' motivation for leaving their homes in order to seek medical treatment [4]. Furthermore, homelessness is more common in patients with schizophrenia, which also reduces their chances of getting proper somatic treatment [28].

Even when treatment for somatic disease is sought, patients with schizophrenia are less likely to receive proper treatment and follow health recommendations. Druss and his colleagues found that patients with schizophrenia were 41% less likely to under cardiac catherization [29]. As far as screening and monitoring procedures are concerned, patients with schizophrenia are also left behind; they are less likely to receive a retinal examination if they have diabetes [30], and fewer female schizophrenia patients receive screening for cervical cancer [31]. Munk-Jorgensen investigated the somatic admission rate ratio (RR) for patients with schizophrenia compared to matched controls for a variety of cardiovascular diagnoses [32]. A reduced contact rate (RR<1) was found for more silent diseases such as arteriosclerosis whereas diseases with clearer symptoms, such as pulmonary edema, were associated with a RR>1. These data seem to suggest that the somatic treatment of patients with schizophrenia is delayed until the somatic disease becomes more serious and shows more symptoms.

It cannot be ruled out that psychiatrists, and perhaps also medical doctors, interpret the medical complaints of patients with schizophrenia as expressions of their delusions or as hallucinations, with the result that medical diseases are not diagnosed before they become life-threatening. An old study by Koranyi found that 43% of patients with schizophrenia also suffered from physical illnesses, of which 46% had not been diagnosed. Non-psychiatrist physicians were found to have missed 33% of the somatic diagnoses, while psychiatrists had missed detecting 50% of the physical illnesses [33]. Such high numbers are worrying and it may be speculated that they are the consequence of a lack of communication skills in relation to psychotic patients on the part of non-psychiatric physicians and poor clinical skills regarding the detection of physical illness on the part of psychiatrists.

The fact that patients with schizophrenia are less likely to seek medical treatment could lead to an underestimation of the prevalence of somatic diseases, simply because they are not diagnosed. On the other hand, many patients with schizophrenia are institutionalized and it could be argued that the patients' regular contact with care persons would ensure a better recognition of their somatic diseases, which could explain some of the increased morbidity found in this patient group [34].

Cardiovascular Disease and Metabolic Syndrome

Cardiovascular disease is the most frequent cause of death in the general population and in patients with schizophrenia. One half of patients in the general population die from coronary heart disease compared to two-thirds in patients with schizophrenia [35].

Figure 13.1 shows the "metabolic highway" with initial weight gain causing obesity and, as suggested in the figure, this should lead to more focus on lifestyle in order to reverse the weight gain and impede further passage up the metabolic highway. Obesity is the cause of increased insulin resistance, which is compensated by hyperinsulinemia. The result may be the development of type II diabetes, which increases the risk of cardiovascular events. The metabolic highway ends in premature death. Several risk factors can speed up the process: smoking, lack of exercise, high LDL cholesterol levels, diabetes and obesity [35]. The risk factors for cardiovascular disease are additive [36]. As mentioned earlier, the metabolic state has worsened during the past decades; in particular, the prevalence of obesity and its typical consequence, type II diabetes, has increased in that period. A study by Allison and co-workers, using a Body Mass Index (BMI)>27 kg/m^2 to define the condition identified obesity in 42% of patients with schizophrenia compared to 27% for the general population) [37]. Moreover, the distribution of fat and the amount of visceral fat in patients with schizophrenia, even in drug-naive patients [38] point to an increased risk. It has also been established that atypical antipsychotics do not influence on fat distribution [39]. But the distribution of body fat is a better predictor than total fat content of coronary heart disease, with visceral fat being the more dangerous [40]. Dyslipidemia is another risk factor for coronary heart disease, with increasing blood levels of cholesterol strongly associated with atherosclerosis [41]. Patients with schizophrenia are more likely to suffer from dyslipidemia, thus 63% of patients participating in the CATIE trial had dyslipidemia, and despite our knowledge that cholesterol-lowering agents are effective for antipsychotic-induced hyperlipidemia [42], treatment with cholesterol lowering agents was as low as 12% [43].

Metabolic syndrome is a cluster of symptoms associated with an increased risk of developing type II diabetes and cardiovascular disease. The Adult Treatment Panel III under the US National Cholesterol Education Program (2001) requires at least three of the following criteria to be met in order to make a diagnosis of metabolic syndrome [44]:

- Central obesity: waist circumference $\geq$ 102 cm or 40 inches (male), $\geq$ 88 cm or 36 inches (female)
- Dyslipidemia: TG $\geq$ 1.7 mmol/L (150 mg/dl)
- Dyslipidemia: HDL-C $<$ 1.0 mmol/L (40 mg/dL (male), $<$ 1.3 mmol/L (50 mg/dL) (female)
- Blood pressure $\geq$ 130/85 mmHg
- Fasting plasma glucose $\geq$ 6.1 mmol/L (110 mg/dl)

Of the patients who took part in the CATIE trial, 51.6% women and 36.0% men fulfilled the NCEP criteria for metabolic syndrome [45] compared to a sample of the US population, 25.1% (women) and 19.7% (men) [46].

Besides its effect on mortality, antipsychotic-induced weight gain also affects the quality of life of patients [47]. Compared to non-obese their non-obese counterparts, obese patients were 13 times more likely to discontinue antipsychotic medication

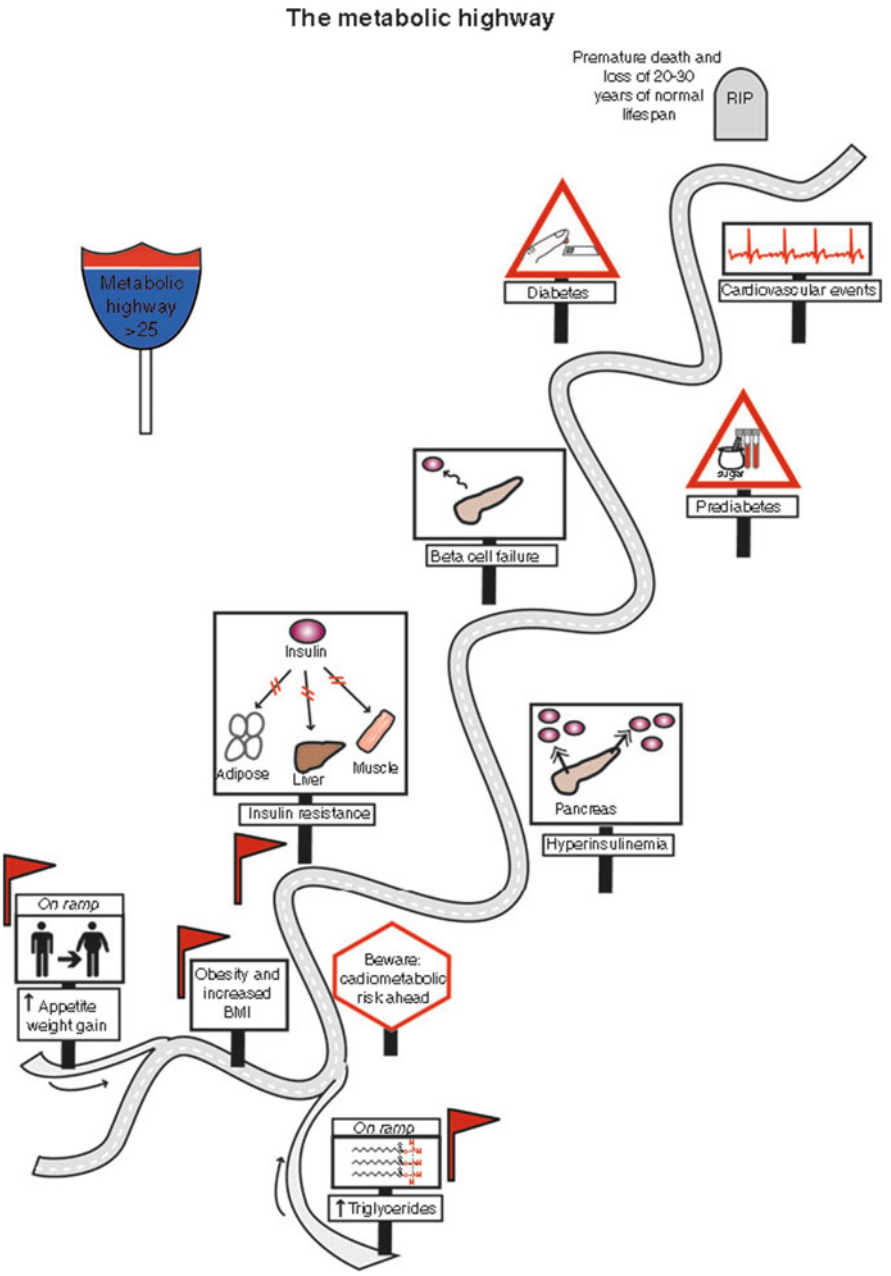

Fig. 13.1 The "metabolic highway" depicts different stages that precede cardiovascular disease and premature death. Increased appetite and weight gain are one on-ramp onto the highway and can lead to obesity and increased boby mass index (BMI). Increased triglycerides can be another way to access the metabolic highway and can lead directly to insulin resistance. The "red flags" along the highway represent the areas that need careful monitoring

[48]. These factors should encourage psychiatrists to prescribe more metabolically safe antipsychotics whenever possible.

The likely outcome of severe weight gain is the development of type II diabetes. Diabetes itself increases the risk of coronary heart disease 2- to 3-fold in men and 3- to 6-fold in women [35]. Patients with schizophrenia are two to three times more likely to develop type II diabetes compared to the general population [49]. Figure 13.2 below shows the prevalence of diabetes in the Canadian population [50]. Type II diabetes in patients with schizophrenia was not only more frequent, but also the onset was earlier compared to the background population, a factor which was more pronounced for female patients. Furthermore, the schizophrenia group had an increased rate of other cardiovascular diseases compared to the background population: heart failure OR: 2.07 (95%CI: 1.98–2.16), stroke OR: 2.17 (95%CI: 2.08–2.26) and myocardial infarction 1.52 (95%CI: 1.48–1.56).

Among the non-modifiable risk factors for type II diabetes are: female sex, African race and advancing age [51]. Weight gain induced by treatment with antipsychotics is considered to be an indirect pathway to the development of diabetes because of its effect of increasing peripheral insulin resistance. The decreased insulin sensitivity is compensated by the secretion of more insulin from the pancreas. However, the compensating effect disappears progressively resulting in increased blood glucose levels, and diabetes sets in. It is important to note that in addition to the indirect pathways to the development of diabetes, studies with olanzapine and clozapine suggest a possible direct adverse effect on glucose homeostasis

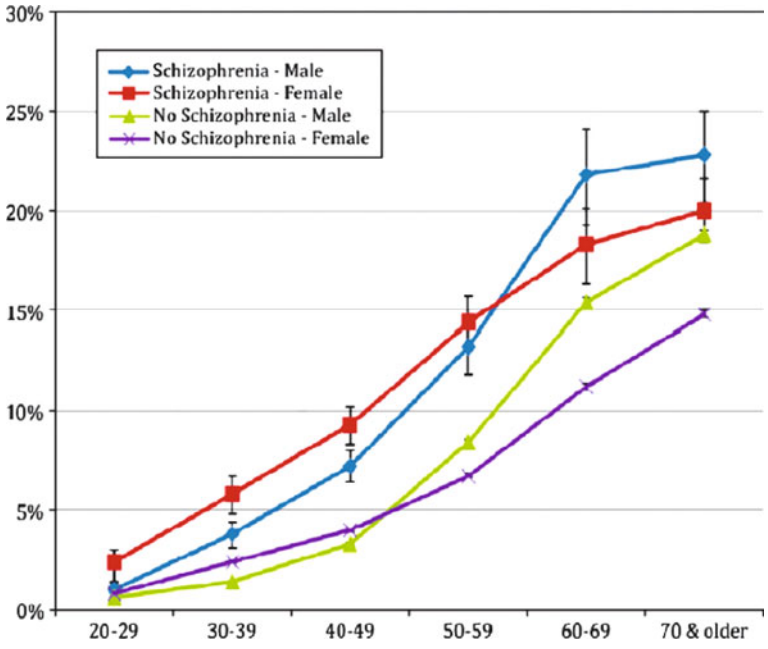

Fig. 13.2 Prevalence of diabetes in people with and without schizophrenia

[52–55]. Most patients who develop diabetes are treated with antipsychotic drugs that involve a high risk for metabolic illnesses, such as olanzapine or clozapine. A surprisingly small number of patients are treated with drugs that pose low metabolic risk [56]. Patients given olanzapine have a 5.8 times increased risk of developing type II diabetes compared to patients who do not receive antipsychotics and 4.2 times compared to patients receiving typical antipsychotics [35]. These striking figures indicate the importance of discussing the choice of antipsychotic medication with patients in order to make them aware of the consequences of treatment with certain antipsychotic drugs. The prescription of medication should always consider the balance between the achieving the desired effect and avoiding unwanted side effects, a general principle which also applies to the psychiatric field.

Early studies suggested that the development of diabetes was not solely a consequence of the treatment of schizophrenia. Data from a study of pre-neuroleptic patients found a higher prevalence of type II diabetes in the patients [57, 58]. However, these finding should be interpreted with caution because the diagnostic criteria for both schizophrenia and diabetes have since been changed. A more recent study by Ryan [59], has found that metabolic changes were present before antipsychotic treatment was initiated. More than 15% of patients had impaired glucose tolerance compared to 0% among the matched healthy controls with no mental disability: (mean = 88.2 mg/dl, SD = 5.4, for the healthy subjects versus mean = 95.8 mg/dl, SD = 16.9, for the patients), insulin (mean = 7.7 μu/ml, SD = 3.7, versus mean = 9.8 μu/ml, SD = 3.9), and cortisol (mean = 303.2 nmol/liter, SD = 10.5, versus mean = 499.4 nmol/liter, SD = 161.4).

As already mentioned, patients with schizophrenia may be predisposed for developing type II diabetes, but whether this reflects a genetic concordance between schizophrenia and type II diabetes [60] or is simply the consequence of poor health habits remains unclear. In the Ryan study, subjects were matched not only for smoking, age and ethnicity but also for their exercise routines as the latter should diminish the effect of poor health habits.

Although in some cases antipsychotic treatment adds to the burden of cardiovascular mortality, this may be balanced with regard to overall mortality. Fontaine and his co-workers estimated that treatment with clozapine caused 416 deaths per 100,000 patients due to weight gain whereas 492 lives were saved because of the anti-suicidal effects of clozapine [61], which is notorious for its potential to cause agranulocytosis, but due to an extensive mandatory hematological monitoring system, only 13 deaths per 100,000 patients were noted.

While the metabolic consequences of antipsychotic treatment are substantial, it is important to remember the consequences of failing to treat these patients. Antipsychotic drugs improve the quality of life of patients' lives and the functional outcome [62, 63]. Another consequence of untreated psychosis is an increased rate of suicide and violent behaviour [64, 65]. Besides, the metabolic effects of antipsychotics are in some cases reversible. Patients who switched from olanzapine to ziprasidone experienced weight loss [66]. The take-home message regarding cardiovascular disease is clear, both for patients and the general population: improving

any of the modifiable risk factors reduces the risk for coronary heart disease dramatically [67, 68]. Smoking cessation reduces the risk by 50%, lowering cholesterol by 10% reduces the risk by 30%, maintaining BMI<25 reduces the risk by 30–55%, and an active lifestyle including walking 20 min every day reduces the risk by 35–55%. As interventions do matter, all patients should be given a thorough examination before they are offered treatment with antipsychotics, including factors such as body weight, waist circumference, fasting plasma glucose, lipids, blood pressure and personal and family history of cardiovascular risk factors – all in order to identify the risk factors and make the necessary interventions [69]. During treatment, body weight should be monitored monthly for the first 3 months and then quarterly. Fasting glucose level, lipids and blood pressure should be checked after 3 months and then annually.

Sudden Death

Another interesting finding, from a cardiac point of view, is that patients with schizophrenia have a higher resting heart rate [70], but the etiology and significance of this remain unknown. Considered as a surrogate marker for the risk of sudden cardiac death, especially after myocardial infarction [71], heart rate variability also seems to play a role as the acceleration and deceleration of the heart beat during inspiration and expiration is known to be associated with treatment with clozapine and olanzapine [72]. But (the the significance of the finding is obscured by the fact that) also drug-naive patients with schizophrenia have been shown to have a reduced heart rate variability [73]. In any event, patients with schizophrenia do have an increased risk of sudden death, but this can be caused by a wide spectrum of conditions which include silent conditions such as epilepsy and cardiac arrhythmia, and also more quantitatively important structural heart diseases such as myocardial infarction. The latter can be identified in an autopsy, but as this is performed on only a few patients, the causes of sudden death typically remain unknown.

Sudden death has been attributed to changes in cardiac repolarization by antipsychotic drugs [74]. Repolarization of the myocytes is measured on a surface ECG as the QT interval corrected for heart rate, giving the QTc interval. A QTc interval >500 ms is associated with an increased risk of developing the form of cardiac arrhythmia known as torsades de pointes (TdP), named due to the rotation of the QRS complexes around the isoelectric line. Several antipsychotic drugs have the effect of prolonging the QTc interval, which increases the potential risk of TdP, but prolongation times differ within the group of antipsychotics. Two atypical antipsychotics, sertindole [75] and ziprasidone [76], have been associated with a prolongation of approximately 20 ms QTc whereas olanzapine prolongs the QTc interval by only 1.7 ms [77]. Furthermore, the relationship between QTc prolongation and cardiac arrhythmia is not entirely clear because some drugs with significant QTc prolongation effect have not been associated with TdP, e.g. ziprasidone. The question is further complicated by the withdrawal of sertindole from the market because of an indication of increased risk of sudden cardiac death due to QTc

prolongation. In 2005, sertindole was reintroduced in most European countries. A large cohort study involving more than 14,000 patient years aiming at investigating the association with sudden cardiac death found no increased overall mortality compared to risperidone but an increased mortality due to cardiac conditions. The increased cardiac mortality was probably balanced due to a decreased risk of suicide [78], which leaves us with the challenge of tailoring antipsychotic medication to each individual patient.

Furthermore, it remains unknown to what extent sudden death is due to drug-induced TdP. A study by Ray and co-workers found that treatment with antipsychotics increased the risk of sudden cardiac death by 2.39 times [79], but it is questionable whether this increased mortality is solely caused by antipsychotic-induced cardiac arrhythmia. It seems more likely that some of the deaths should be attributed to structural heart diseases, e.g. myocardial infarction. In contrast, a Finnish study, including 66,881 antipsychotic users, found that antipsychotic treatment did not increase the risk of death compared to non-treatment [1]. A striking finding in that study was that olanzapine and clozapine were not associated with an increased risk of overall death or cardiovascular death. Otherwise, the largest weight gains and greatest potential to cause type II diabetes are usually ascribed to olanzapine and clozapine. Furthermore, clozapine is used for patients with treatment-resistant schizophrenia, a subgroup of patients whose life style is perhaps even more sedentary than that of the whole group of patients. This suggests that untreated or sub-optimally treated psychosis itself increases cardiovascular mortality. However, several critical appraisals of the study have suggested that the results were an artefact of the study design [80]. In addition, this study did not replicate the Saha group's finding of an increasing mortality rate over the past decades for antipsychotic users compared to non-users [3]. Antipsychotic polypharmacy is common in patients with schizophrenia, but a recent Danish study did not show an increased risk of death in the polypharmacy group compared to the monotherapy group [81].

Cardiomyopathy and Myocarditis

In contrast to factors such as weight gain and diabetes, a number of cardiac conditions can apparently be attributed solely to antipsychotic treatment. Clozapine has the potential to cause two rare side-effects: myocarditis and cardiomyopathy, medical conditions which rarely occur in schizophrenia patients with no exposure to clozapine. Myocarditis is an inflammation of myocardial cells and clozapine-induced myocarditis is probably due to a type 3 immunoglobulin E-mediated allergic reaction. However, a direct toxic effect of clozapine [82] and a low selenium level induced by clozapine has also been suggested to be the mechanism. Myocarditis occurs during the initial stages of treatment with clozapine, 79% within the first 6 weeks of treatment, with influenza-like febrile symptoms, sinus tachycardia, palpitations and fatigue. ECG characteristics are the elevation of the ST segment. The incidence of clozapine-induced myocarditis is 1 out of 500 patients

with mortality as high as 50% [82]. Myocarditis is best diagnosed by measuring the blood levels of troponin as its levels rise in case of myocardial damage.

Dilated cardiomyopathy occurs after months of exposure to clozapine, 65% after 6 months of treatment, and presents a more difficult diagnostic case as its early phases can only be verified by echocardiography [83]. The incidence of clozapine-induced cardiomyopathy is estimated to be 51.5 per 100,000 patients, a five-fold increase compared to the background population [82]. The mechanism remains largely unknown, but persistent sinus tachycardia may be involved or a direct toxic effect of clozapine mediated by free radicals. The symptoms are those related to heart failure: exertional dyspnea, fatigue, peripheral edema, orthopena and chest pain. If cardiomyopathy is suspected, patients should be referred for an echocardiography.

Cancer

The relationship between schizophrenia and cancer morbidity and mortality has been an epidemiologically puzzle for decades. As early as the beginning of the twentieth century, a reduced risk of cancer was found in patients with schizophrenia [4]. There has been some speculation as to whether the genetics of schizophrenia somehow provide protection against the development of cancer. It has been speculated that the polymorphism of the tumor-suppressor gene, p53, central to the regulation of apoptosis and specifically found in patients with schizophrenia, might reduce the risk of lung cancer [84, 85]. If this is the case, the question would be whether parents and siblings of patients with schizophrenia also have a reduced risk of cancer, and Levav and co-workers found a reduced risk among parents and siblings [86]. In contrast, a Danish study saw no reduction in risk among relatives of patients with schizophrenia [87]. In general, there is no consistency within this field. Large epidemiological studies have shown inconclusive results for rates in overall and specific cancers in this population. Various studies have found both increased and decreased cancer risks in patients with schizophrenia [88, 89]. In Israel, over a 10-year period, the cancer rate in patients with schizophrenia was 42% lower than in the general population [90], but the same study detected an increased risk of breast and lung cancers. In a Finnish study [34], a 17% increased risk for overall cancer was found, but half of the excess cases were due to lung cancer. In contrast, the study identified a 9% reduced risk in parents and an 11% reduced risk in siblings compared to the general population.

There are several reasons for the uncertainty as to whether patients with schizophrenia are more prone to develop cancer. Cancer is a relatively rare event and therefore a large sample size is needed to detect a difference between the two groups. Large sample sizes are usually derived from linking national databases. Such samples are often drawn from Scandinavia because every individual citizen has a personal ID number, and the Scandinavian countries have a long tradition for keeping national databases, making it possible to link and access data about individuals from several databases. The etiology of cancer is, however, multi-factorial

and, as already described, the lifestyle of patients with schizophrenia differs from the lifestyle of the general population. Comparing the incidence of cancer in these two groups would demand the possibility of adjusting for several covariates such as age, sex, smoking, substance abuse and eating habits. Besides the covariates known to be associated with cancer development, there may be several unknown risk factors. Even an extensive linkage of databases would not allow for the complete adjustment of these differences in the statistical analyses. The detection rate of cancers might furthermore be different between patients with schizophrenia and the general population because patients with schizophrenia do not seek medical help to the same extent as the general population (see Section "Access to Somatic Treatment"). Finally, the autopsy rate could also be different, giving a risk of attributing more or fewer cases of clinically unknown cancers to one of the groups [34].

The use of antipsychotics could have the effect of increasing the rate of breast cancer because of the antagonistic effect on the dopamine receptors. Dopamine inhibits the secretion of the prolactin hormone from the pituitary gland and therefore dopamine antagonists lead to the secretion of prolactin. By nature the prolactin level is high during breast feeding. Hyperprolactinemia may cause galactorrhea, amenorrhea and gynecomastia, with osteoporosis as a long-term adverse effect [91]. The high level of circulating prolactin has been associated with an increased risk of breast cancer in preclinical studies [92–94] and in a few large epidemiological studies [95, 96]. Wang and his colleagues [96] found an increased risk of breast cancer in patients taking dopamine antagonists, i.e. antipsychotics and antiemetics, suggesting the antagonism on the dopamine receptor to be the common mechanism. However, negative studies exist [97–100], and there is still no general agreement that dopamine antagonists, in this case antipsychotics, increase the risk of breast cancer [91].

Another issue is the fact that the reduced lifespan of patients with schizophrenia might bias the cause of death, i.e. patients who die from coronary heart disease at age 50 might have died from cancer 15 years later, if they had lived longer. The risk of cancer increases with age and so does the cancer mortality rate [101], cancer rates should therefore always be adjusted for age.

In conclusion, it still remains largely unknown whether patients with schizophrenia have a decreased risk of developing cancer and what influence schizophrenia as a disease in itself and its treatment have on the incidence.

Venous Thromboembolism

Untreated deep venous thrombosis (DVT) may lead to pulmonary embolism, a potentially fatal condition. Risk factors for DVT are advancing age, immobilization, oral contraceptives, obesity and pregnancy [102]. Schizophrenia as a disease has itself also been associated with an increased risk of DVT [103, 104]. Furthermore, physical impediments are also thought to induce a higher risk of DVT [105].

Antipsychotic treatment, especially clozapine and low potency antipsychotic drugs, has been connected with an increased risk of DVT [106, 107]. The mechanism of antipsychotic-induced DVT or the relation to the underlying disorder remains unknown, but it has been speculated that the sedating properties of the drugs could be involved. Sedative drugs might cause immobilization and thereby venous stasis. The suspicion that the sedative properties of the drugs are involved is supported by the fact that the most sedative drugs, e.g. clozapine and low-potency antipsychotics, are those that carry the highest risk of DVT. Circulating antiphospholipid antibodies are associated with an increased risk of thrombosis, and increased levels of antibodies have been found in patients undergoing treatment with clozapine [108], but they have also been found in drug-naive psychotic patients [109]. Finally, the increased adrenaline secretion that occurs during psychotic excitation has also been associated with enhanced blood coagulation [102].

In conclusion, on a par with other conditions described in this chapter, we must say there is a need for well-designed studies investigating whether this increased occurrence of DVT is due to the treatment, the schizophrenia disease itself, or the unhealthy lifestyle of patients with schizophrenia.

Movement Disorder

The first antipsychotic drug, chlorpromazine, was introduced in 1954, and a few years later it became clear that treatment with antipsychotics could induce involuntary movements, called tardive dyskinesia. Beside tardive dyskinesia, which is considered a long-term side-effect of treatment with antipsychotic drugs, a wide range of movement disorders has been associated with antipsychotic treatment. These antipsychotic-induced movement disorders due to the dysregulation of dopamine in the basal ganglia are known as extra pyramidal side-effects (EPS). Normal motor function depends on the transmission of dopamine and acetylcholine. Antipsychotic treatment causes a hypodopaminergic state in the basal ganglia which become relatively lower compared to the cholinergic transmission. The imbalance between the two neurotransmitters gives EPS side effects such as bradykinesia and rigidity. EPS can be reversed by lowering the antipsychotic dose, thereby reducing the hypodopaminergic state, or it can be reversed by reducing the cholinergic transmission by the addition of an atropine-like (anticholinergic) drug to balance the hypodopaminergic effects of antipsychotics.

Schizophrenia itself has also been associated with movement disorders, e.g. catatonic symptoms and neurological soft signs appearing even before the onset of psychotic symptoms. These symptoms can be difficult to distinguish clinically from antipsychotic-induced movement disorders due to the concurrent presence of both antipsychotic treatment and the schizophrenia disease. Spontaneous dyskinesia has been found in 16.9% of antipsychotic-naive patients with schizophrenia [110] and was correlated with more negative symptoms and poorer treatment outcome. On the other hand, neurological soft signs such as motor coordination and right/left spatial

orientation have also been associated with negative symptoms, and antipsychotic treatment seems to improve the neurological soft signs [111]. The neurological soft signs are correlated with anatomical findings by MR scanning [112] and the deterioration of some of the domains of neurological soft signs, e.g. motor coordination impairment, has been found in non-psychotic siblings [113]. Even though it has been assumed that neurological soft signs are a core feature of the disease, they do not seem to be associated with cognition, which constitutes another core feature of schizophrenia [114]. Deficient cognitive abilities are more consistently found in the whole course of the disease [115], whereas neurological soft signs seem to improve during antipsychotic treatment [111]. Furthermore, improvement in neurological soft signs seems to be correlated with a better outcome, but the use of neurological soft signs as a predictor requires further investigation.

Catatonia is a motor dysregulation syndrome inhibiting patients from normal movement despite intact physical capacity [116]. There are several features associated with catatonia such as mannerism, waxy flexibility, stupor, stereotypy, negativism or posturing. Catatonic syndrome is considered to be a response to a medical or mental condition, but even though objective similarities between catatonia and EPS, e.g. stereotypy and antipsychotic-induced tardive dyskinesia or posturing and antipsychotic-induced dystonia, the rate of catatonia has been declining over the last 50 years. It remains unclear whether this is due to the introduction of antipsychotic drugs.

Another interesting complication of the catatonia and antipsychotic-induced movement disorder is malignant catatonia (MC), which seems to appear in a drug-induced variant called neuroleptic malignant syndrome (NMS) [117]. The two syndromes are practically indistinguishable [116], and both are characterized by the following symptoms: fever, Parkinsonism, altered consciousness and autonomic instability, i.e. labile blood pressure and heart rate. As a consequence of muscle rigidity and hyperthermia, significant elevated levels of serum creatinine kinase are found. Other laboratory abnormalities are present, such as leukocytosis and decreased serum iron, none of which is specific to the diagnosis. The only clinical difference between the two syndromes is that an NMS diagnosis can only be established shortly after the administration of an antipsychotic drug. The pathophysiology of the syndromes is thought to be due to a dysregulation in the circuits between the motor cortex and the basal ganglia [118]. However, the exact pathophysiology remains unknown. Both syndromes are potentially fatal and the recommended treatment is the discontinuation of antipsychotic treatment, high dose benzodiazepines and dopamine agonists. In more refractory cases ECT can be used with success. Dantrolene is often used to reduce hyperthermia and muscle rigidity. Sufficient fluid therapy is essential to prevent damage to the kidneys due to the breakdown of muscle cells.

Movement disorders among patient with schizophrenia are still frequently observed. In many cases it is difficult to establish the etiology. The introduction of atypical antipsychotics have not brought about the disappearance of EPS [119] and psychiatrists should still focus on the identification and management of these unfortunate side-effects.

Conclusion and Clinical Recommendations

One of the aims of this chapter was to discuss whether the increased presence of somatic illness is a consequence of the schizophrenia disease or of its treatment. Firstly, establishing the exact incidence and prevalence of somatic disease in this patient group is uncertain because patients with schizophrenia show a different pattern for seeking medical help, thus influencing the observed rates of somatic diseases. As far as the majority of the diseases are concerned, it is not possible to determine the exact contribution made by schizophrenia or by its treatment because both the treatment and the disease seem to be involved. It would take a long-term double-blinded, randomized, placebo-controlled study involving a long-term exposure of healthy volunteers to antipsychotics to determine the effects of schizophrenia and antipsychotics on health, but a study with the described design would naturally be unethical.

Regardless of the etiology of their poor physical health status, the physical health of patients with schizophrenia should be given special attention by every psychiatrist and physician. Psychiatrists should focus more on asking patients about their physical health and encourage them to lead more healthy and active lives. Furthermore, psychiatrists have the responsibility to ensure that all patients treated with antipsychotic drugs are screened for metabolic syndrome, diabetes and dyslipidemia at a minimum of once a year. Lifestyle and medical interventions similar to those offered to the background population should be offered to this patient group. Patients should receive adequate antipsychotic treatment with preference for those antipsychotic drugs that cause the fewest metabolic side-effects.

Physicians are required to meet schizophrenia patients with the same attitude and willingness to help as they do every other patient. Furthermore, physicians should learn more about schizophrenia and how to interview patients with schizophrenia. In order to succeed in the challenging task of treating somatic comorbidity in patients with schizophrenia, psychiatrists and physicians must work in close collaboration.

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Chapter 14
The Interface of Cannabis Misuse and Schizophrenia-Spectrum Disorders

Claire E. Ramsay and Michael T. Compton

Abstract This chapter provides an overview of the complex ways in which cannabis misuse intersects with schizophrenia-spectrum disorders. The centrally active constituents of *Cannabis sativa* are discussed, and the central endocannabinoid system is briefly reviewed. Information on cannabis use and misuse in the general population is provided, including the prevalence of use in general population samples and consequences of such use. Findings pertaining to cannabis misuse among individuals with schizophrenia-spectrum disorders are presented, along with an overview of the adverse effects of cannabis use in terms of symptoms, neurocognition, age at onset, and various aspects of the long-term course and outcomes. A discussion of the literature that suggests that cannabis use is a component cause of, or independent risk factor for, psychosis is given. Other potential mechanisms for the association are considered, including psychosis causing cannabis use or the existence of a shared diathesis that underlies both. To evaluate the literature suggesting that cannabis use, especially in early adolescence, is a component cause of schizophrenia-spectrum disorders, nine criteria for establishing causality are summarized. The chapter concludes with a brief discussion of treatment implications for clinicians and program developers, as well as prevention implications for researchers, public health officials, and policy-makers.

Keywords Cannabis · Endocannabinoid · Marijuana · Psychosis · Schizophrenia · Substance abuse

Abbreviations

Δ^9 -THC	Delta-9-tetrahydrocannabinol
CBD	Cannabidiol
CI	Confidence interval

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CNS	Central nervous system
OR	Odds ratio
US	United States

Introduction

Western societies have had a long and complex relationship with marijuana, or cannabis, at times tending to propagandize the adverse consequences of using the drug, and at other times and in other places striving to promote the drug as benign or even beneficial [1, 2]. Within the last two decades or so, however, there appears to have been a gradual accumulation of psychiatric and neurobiological evidence that cannabis use may in fact be detrimental in some mental health domains. This is true of the psychosis continuum, spanning from psychotic-like symptoms in the general population, to schizotypal personality traits, to the initial onset of psychotic disorders, to the long-term course of chronic psychotic illnesses. A general summary of the relevant research literature, as provided in this chapter, clearly indicates that cannabis use is intimately tied to psychosis in a number of ways. There is now convincing evidence that premorbid cannabis use is likely a component cause – part of a complex constellation of risk factors – of schizophrenia-spectrum disorders.

Researchers have repeatedly found themselves, after careful reviews of the extant literature, or upon completing rigorously conducted studies, concluding their articles with admonishments that policy-makers and public health officials should not ignore the clear signal of science indicating that cannabis use, especially in early adolescence, increases risk for psychotic disorders [3–7]. There has seemed to be a need to defend these results, which challenge widely held assumptions, and at times vocal insistence, that this "soft" drug is neither addictive nor harmful. Although its addictive potential is now quite clear (e.g., a cannabis withdrawal syndrome is now widely recognized [8]), there may indeed be some individuals in the population who experience few or no adverse consequences to occasional or light use. However, this chapter presents a case for cannabis use being detrimental in several respects for those with psychotic disorders or individuals with an underlying, latent vulnerability to developing such illnesses.

It would appear that the convergence of evidence is now such that society at large may be interested in learning more, as exemplified by the July 2010 article in *Time* magazine entitled "The Link Between Marijuana and Schizophrenia" [9]. This chapter attempts to present a balanced view of the complex interface; while recognizing that the associations between cannabis use and psychosis (and between psychosis and cannabis use) are undoubtedly multi-faceted, perhaps too complicated for a brief chapter to adequately portray even in the most general of ways. For this reason, many of the most pertinent references are provided. For a much more in-depth review of many of the topics covered in this brief chapter, the 2004 book *Marijuana and Madness: Psychiatry and Neurobiology*, by Castle and Murray [10] is highly recommended.

The Plant, Methods of Intake, and Centrally Active Constituents

While it grows wild and is also cultivated worldwide, cannabis is native to central Asia, where it originally grew near riverbeds and on hillsides [11]. This flowering plant has been cultivated widely for centuries, valued for its ability to produce fibers, oil, and Δ-9-tetrahydrocannabinol (Δ^9-THC) a substance producing euphoric effects. Although it has gone through substantial changes due to artificial selection, the domesticated cannabis plant has never become dependent on humans and strains have often escaped to grow wild. There are three known species, two of which – *Cannabis sativa* and *Cannabis indica* – are used to produce cannabis-based euphoric drugs [11, 12].

Δ^9-THC is extracted from the cannabis plant in three different forms: herb, resin (or hashish), and oil [12]. The herb form consists of the flowering tops of the cannabis plant, which are dried and can be smoked in cigarette or cigar form (called joints and blunts) respectively, or in a variety of pipes. Approximately 79% of cannabis confiscations consist of the herb form, suggesting that this is the most prevalent form in use, and most cannabis herb seizures come from the United States (US; 60%) or Africa (30%) [12]. Cannabis resin, or hashish, is comprised of resin secretions from the female plant, made during the flowering phase of the plant's development. This form of cannabis is most popular in Europe, and is typically mixed with tobacco and smoked [12]. Cannabinoids can also be extracted from the herb or resin form into an oil or butter-based solution, which can then be used to make food products.

Although the plant produces over 60 cannabinoids, Δ^9-THC is the psychoactive constituent that appears to be responsible for the euphoric effects of the substance [13]. This compound is lipid soluble and can activate cannabinoid receptors in various regions of the brain, as reviewed in more detail below. When consumed, Δ^9-THC produces a euphoric effect or "high," but also may result in at least two other well defined psychological state changes: derealization of self and surroundings, and an anxious/depressive state [14]. Cannabis use can also result in perceptual changes, such that colors become brighter, music more vivid, and time appears to go faster [13]. Physiological effects include increased diastolic blood pressure; decreased body temperature [14]; an increased heart rate; greater expired carbon monoxide [15]; and in the long-term, respiratory problems and reduced lung tissue density [16]. Over the past 20 years, plant-breeding techniques have greatly increased the potency of cannabis products; whereas a typical "reefer" of the 1960s and 1970s contained approximately 10 mg of Δ^9-THC, a modern-day "joint" made from potent subspecies may contain 150 mg, or even 300 mg if it is laced with hashish oil [13].

Of note, aside from the major psychotropic constituent of exogenous cannabinoids (Δ^9-THC), there has been increasing interest in cannabidiol (CBD), which is thought to have anxiolytic properties, and perhaps even antipsychotic effects. That is, interestingly, the two main agents in ingested cannabis appear to have quite opposing actions: Δ^9-THC is psychotomimetic, whereas CBD may have antipsychotic effects [17]. CBD, the second most abundant constituent of *Cannabis*

sativa, has weak partial antagonist properties at the CB_1 receptor (see below), inhibits the reuptake and hydrolysis of anandamide, and exhibits neuroprotective antioxidant activity [18]. This cannabinoid displays diverse pharmacologic actions (e.g., anticonvulsive, sedative, hypnotic, anti-inflammatory, neuroprotective, and possibly antipsychotic) without significant intrinsic activity on cannabinoid receptors; thus, it does not produce the psychotropic effects of Δ^9-THC [19]. It has been suggested that CBD may have antipsychotic properties [20, 21], largely based on its effects in animal models of psychosis, findings from a small body of pre-clinical data, and results of very early clinical reports. Further research is needed, and the anxiolytic and other central nervous system (CNS)-related properties of CBD and other phytocannabinoids are being actively studied [19, 22].

The Central Endocannabinoid System

Whereas the major psychotropic constituent of exogenous cannabis is Δ^9-THC, the major "endocannabinoid" (normal physiological compound that binds to the same receptors to which Δ^9-THC binds) is anandamide. Although thousands of papers on the pharmacology and clinical effects of Δ^9-THC and related compounds have been published since 1964 when Δ^9-THC was identified [23], less is known about anandamide and related endocannabinoids. In 1988, specific, high-affinity cannabinoid binding sites were discovered in the rat brain [24], referred to as the CB_1 receptor. The peripheral CB_2 receptor was identified in mouse spleen several years later [25]. Thus, the CB_1 receptor is generally, though not exclusively, a "neuronal" receptor, whereas CB_2 is largely an "immune system" receptor [26]. After the discovery of the CB_1 receptor, it was assumed that the presence of a specific cannabinoid receptor in the CNS indicated the existence of endogenous cannabinoid ligands that activate such receptors [23]. Once identified [27], that compound was dubbed *anandamide* based on the Sanskrit word for bliss, and due to its chemical nature [23]. The discovery of other endocannabinoids that bind to the CB_1 receptor soon followed, though less is generally known about those ligands.

The biosynthesis and metabolism of anandamide and other endocannabinoids, such as 2-arachidonoyl glycerol, are now extensively understood [28, 29]. Anandamide is not stored in cells, but is rather formed mainly when needed, and it is inactivated in the brain by both reuptake and enzymatic hydrolysis [23]. Research on the endocannabinoid system has resulted in the identification of inhibitors of anandamide reuptake; compounds that block fatty acid amide hydrolase, the enzyme that hydrolyses anandamide; synthetic cannabinoids that are much more potent than Δ^9-THC and related compounds; agonists specific to CB_1 or CB_2 receptors; and specific antagonists. As an example of the latter, rimonabant (SR141716) selectively blocks CB_1 receptors [30], and has been studied as a potential anti-obesity agent [31]. In fact, rimonabant has been approved in several countries as a medication to reduce body weight and improve cardiovascular risk factors in obese adults [18, 32]. Like CBD, rimonabant has recently been shown to have antipsychotic properties in

both animal and human models used to assess antipsychotic activity, as reviewed by Roser and colleagues [18].

CB_1 receptors are mainly located on presynaptic axons and nerve terminals, consistent with the role of endocannabinoids in modulating the release of diverse neurotransmitters. High densities of these receptors are located in the cerebral cortex (especially frontal regions), limbic forebrain (particularly in the hypothalamus and anterior cingulate cortex), hippocampus, basal ganglia, and cerebellum [33]. After endocannabinoids bind and activate CB_1 receptors, they are largely degraded by several enzymes, such as fatty acid amide hydrolase. Whereas exogenous cannabinoids (typified by Δ^9-THC) cause a long-lasting activation of CB_1 receptors and thus a persistent inhibition of neurotransmitter release from nerve terminals that express such receptors, endocannabinoids (exemplified by anandamide) have inhibitory effects in a discrete local region for tens of seconds in response to particular patterns of afferent inputs [33].

It is likely that dysregulation of the central endocannabinoid system leads to specific symptoms or disorders, thus potentially contributing to the biological basis of some neurological and psychiatric illnesses [23]. In fact, several potential abnormalities in the endocannabinoid system have been reported among individuals with schizophrenia. For example, as presented in greater detail by Sundram and associates [34], Leweke and coworkers [35] found elevated levels of anandamide in the cerebrospinal fluid of 10 patients with schizophrenia compared to 11 controls. These elevated anandamide levels, which appear to be negatively correlated with psychotic symptoms, may point to a protective role, whereas the role of 2-arachidonoyl glycerol remains unclear [21]. Other examples of endocannabinoid abnormalities that have been reported in schizophrenia include an elevated density of CB_1 receptors in the prefrontal cortex in a post-mortem study involving 14 patients and 14 controls [36], and differences in a triplet repeat polymorphism in the CB_1 receptor gene among 242 Japanese patients and 296 controls [37]. Another preliminary study found that a single-base polymorphism in the CB_1 receptor gene was associated with varying risk of substance abuse among individuals with schizophrenia [38]. Of note, associations between genetic polymorphisms in the endocannabinoid system and schizophrenia have been quite mixed, as reviewed elsewhere [26, 39]. These and other studies [40–43] indicate possible endocannabinoid system alterations in schizophrenia that could be related not only to increased risk for schizophrenia, but also an elevated propensity for cannabis use [44].

Further research is needed to tease apart specific aspects of inherent dysregulation of the endocannabinoid system associated with schizophrenia from responses to exogenous cannabinoids or antipsychotic medications. D'Souza et al. [45] distinguished the "exogenous hypothesis," in which cannabinoids like Δ^9-THC produce psychotic disorders by mechanisms extrinsic to the pathophysiology of naturally occurring psychoses, from the "endogenous hypothesis," in which components of the endocannabinoid system (like CB_1 receptors) are dysfunctional, contributing to the pathophysiology of schizophrenia (or some subtypes of this heterogeneous diagnostic category), perhaps unrelated to cannabinoid ingestion. Furthermore, they note the existence of diverse research findings that tentatively support both of these hypotheses.

Cannabis Use and Misuse in the General Population

Prevalence of Cannabis Misuse in the General Population

The first written recording on cannabis dates to 2727 BCE, when cannabis was used for medicinal purposes and was already reported to cause hallucinations if used in excess [1]. Cannabis has been used medicinally in various regions of the world since then, and its use came under debate as early as 900 CE; though it was not until the 1900s that governments started to outlaw its production and use [46]. Cannabis extracts were classified as a narcotic drug in the 1961 United Nations Single Convention on Narcotic Drugs, which served to update and standardize multi-lateral treaties on all narcotics, calling for participating countries to limit production, exportation, importation, distribution, possession, and use of cannabis exclusively to medical and scientific purposes [47]. Some 97 countries were represented in the original convention, and in total 184 have joined this treaty [48], making cannabis an illicit substance in most countries, though with varying degrees of prohibition and enforcement. While cannabis use is restricted or illegal in most areas, its production and use are not declining. For example, during the period from the late 1990s to 2006, there was a 10% increase in global cannabis consumption [12].

Currently, cannabis is the most widely used illicit drug worldwide. It is produced in at least 176 countries and consumed by approximately 4% of the world's population in a given year [12]. The annual prevalence of cannabis use is highest in Oceania (15.4%), followed by North America (10.3%), Africa (8.1%) and Western Europe (7.4%) [12]. Cannabis use is least prevalent in Asia (2.1%), Southeast Europe (2.3%) and South America (2.6%) [12]. Globally, cannabis use is associated with certain demographic characteristics, including male gender, a secondary or higher education, single or divorced marital status and a higher income [49]. The initiation of cannabis use typically occurs between the ages of 16 and 19 years, and in many areas of the world, younger adults are more likely to report having used the substance than are older adults, suggesting that the incidence of cannabis use may be increasing [49]. Interestingly, in recent years, younger women are much more likely to report having used cannabis than in previous years, effectively beginning to close the gender gap in younger cohorts [49].

Consequences of Cannabis Misuse in the General Population

Cannabis Abuse and Dependence

In the population at large, one of the most immediate consequences of cannabis use is that a portion of users develop a cannabis use disorder – currently described as cannabis abuse or cannabis dependence – such that they lose control over their cannabis use, neglect important areas of their lives, or put themselves or others in harm's way [50]. Data on the prevalence of cannabis use disorders is limited or

non-existent in many countries but is available in the US and Australia, two countries with relatively high rates of cannabis use. While the portion of the US population using cannabis remained stable at approximately 4% during the 1990s, the rate of cannabis use disorders increased from 1.2% in 1990–1991 to 1.5% in 2000–2001 [51]. In the US, the lifetime and 12-month prevalences of cannabis abuse (7.2 and 1.1%) exceed those of cannabis dependence (1.3 and 0.3%) [52]. Similar rates were reported in Australia, where 1.7% of respondents in a nationally representative household survey met criteria for a cannabis use disorder [53].

In the US, cannabis use disorders are more prevalent among those who are single, separated, divorced, or widowed, and rates vary by geographic region and ethnicity, with a higher prevalence among Native Americans and lower rates among African Americans, Asian Americans, and Hispanic Americans in comparison to Caucasians [52]. The mean ages at onset of cannabis abuse and dependence in a US sample were 19.3 and 19.0 years, with an average duration of 35.0 and 44.3 months, respectively [52]. In the US, treatment seeking is relatively low for cannabis abuse (9.8%) and dependence (34.7%) and is delayed by an average of 5.5 and 3.0 years, respectively, after onset of the disorder [52].

Cannabis use disorders are associated with high rates of psychiatric comorbidities. In a large, nationally representative sample in the US, a substantial portion of those with a cannabis use disorder in the past 12 months also had a current alcohol use disorder (57.6%), nicotine dependence (53.1%), a mood disorder (29.9%), an anxiety disorder (24.1%), and/or a lifetime history of a personality disorder (48.4%) [52]. In a similar study from Australia, those with a 12-month history of cannabis dependence were more likely to have an anxiety disorder (odds ratio (OR): 1.4), a positive screen for psychosis (OR: 2.8), or another drug use disorder (OR: 14.0), but were less likely to have a mood disorder (OR: 0.9), after adjusting for age, gender, educational attainment, marital status, employment status, and neuroticism [54]. Among those with cannabis dependence, the unadjusted rates of affective (13.6%) and anxiety (16.5%) disorders, a positive screen for psychosis (6.8%), and another drug use disorder (17.6%) were higher than among those with no cannabis use during the past year (6.2%, 5.4%, 0.7%, and 0.5%, respectively) [54].

Impaired Academic Performance

Cannabis use and misuse are consistently associated with poor school performance in a wide range of adolescent and young adult samples. The intensity of cannabis use is correlated with lower grade point averages, less satisfaction with school, negative attitudes about school, and non-attendance [55]. In a study of three Australian cohorts, cannabis use at 15 years of age was predictive of school non-completion [56]. Multiple theories have been proposed to explain this association, including the ideas that cannabis induces an "amotivational syndrome," causes cognitive impairments, or is used mostly by those youths who have adopted an anti-conventional (e.g., rebellious) lifestyle [55]. The latter theory appears to have the strongest support [57, 58]. For instance, the effects of cannabis use on school attendance and

performance were reduced, but not altogether absent, when variables such as adolescents' tendency towards a social/delinquent lifestyle and family structure were controlled for [57]. A recent study found that low school performance at the age of 14 years is a predictor of frequent cannabis use in young adulthood, which suggests that this association may well be bi-directional [59].

Criminal Behavior, Suicidality, and Unintentional Injuries

Societal impacts of cannabis use include associations with criminality, suicidality, and vehicular accidents [58, 60]. In a longitudinal study in New Zealand, the frequency of cannabis use correlated with higher instances of property/violent crime, even after controlling for adverse life events, deviant peer affiliations, school dropout, living situation, and other substance use [60]. An analysis of police records in the US revealed a positive association between self-reported cannabis use at the time of the offense and non-drug related violent, property, and income-producing crime, after controlling for other substance use [61]. Similarly, the use of marijuana or other drugs, peer use of illicit substances, and family members' use of illicit substances were each independently associated with a higher likelihood of committing violence among Colombian adolescents [62]. Suicidal ideation and suicide attempts are also associated with cannabis use, especially in young adolescents, though this effect is reduced and does not always remain significant after controlling for demographic and other relevant variables [60, 63, 64]. Also of concern, the effects of acute cannabis intoxication include cognitive and psychomotor impairments that reduce individuals' ability to operate a vehicle safely, especially when sustained attention is necessary [58]. In laboratory simulations, the effects of recreational doses result in an impairment that is comparable to blood alcohol levels of 0.07–0.10%, though in more realistic test settings, cannabis users appear to be aware of their impairment and are less likely to take risks than alcohol users [58].

Impairments in Neurocognition

Cannabis use also affects cognitive functioning in multiple domains, such as short-term memory and attention [65], as well as working memory [66, 67]. These deficits also have been observed in animal studies [68, 69], and have been assessed using both electroencephalography [70] and functional magnetic resonance imaging [71] in addition to neuropsychological methods. The longer-term consequences on cognitive functioning are less clear. Long-term cannabis users performed more poorly than controls or short-term users in a measure of verbal learning, and made more errors than the other groups in a measure of verbal information processing [72]. In a Costa Rican sample, long-term cannabis use was associated with impairments in short-term memory, working memory, and attention, but only when comparing an older cohort of users with non-users; no differences between younger users and non-users were evident [73]. The association of long-term cannabis use with impaired learning and working memory has appeared to be replicated [71, 74]. However,

other studies have failed to detect long-term cognitive consequences of cannabis use [75].

Psychotomimetic Effects and Psychiatric Symptoms

The psychotropic effects of cannabis on any particular individual vary somewhat in relation to diverse factors – strain of the plant, part of the plant ingested, route of administration, proportional content of Δ^9-THC, dose consumed, previous experience, expectation of effect, personal characteristics of the individual, and the context in which the agent is taken [76] – but tend to be relatively consistent in terms of the typical euphoric effects mentioned above. Yet, cannabis intoxication can at times result in depersonalization and derealization, enhanced self-observation, disjointed speech, visual and auditory hallucinations (though usually poorly formed and short-lasting), and grandiose and paranoid ideation of nearly delusional proportions. Cannabis ingestion also has the potential to induce or alleviate anxiety, perhaps related to the dose taken and the proportional content of CBD. There is ongoing debate about whether long-term cannabis use induces a syndrome of amotivation reminiscent of the negative syndrome commonly observed in schizophrenia [58, 76]. Clearly, a number of the psychotropic effects of cannabis are recognizably similar to the signs and symptoms of schizophrenia and related psychotic disorders.

Cannabis-Induced Psychosis

In a small subset of individuals who ingest the substance, a short-lasting psychotic syndrome may occur. These individuals would be diagnosed as having a cannabis-induced psychotic disorder if there is a clear temporal relation between heavy drug intake and the onset of psychotic symptoms, as well as rapid and complete resolution of symptoms after abstinence; furthermore, such a diagnosis assumes that the psychosis would not have occurred in the absence of cannabis use. A number of case reports of cannabis-induced psychosis can be found in the literature [77], though conclusions drawn from case reports are inherently limited. It remains debated as to the extent that cannabis use can cause a "cannabis psychosis" that is etiologically distinct from most schizophrenia-spectrum disorders.

Some have argued that a cannabis-induced psychosis might in many instances be an early sign of schizophrenia rather than a distinct clinical entity [78]. In fact, in one study that followed patients treated for cannabis-induced psychosis in Denmark, nearly 50% received a diagnosis of a schizophrenia-spectrum disorder within a mean follow-up period of 5.9 years [79]. Crebbin and colleagues [80] reported that among 35 first-episode psychosis patients diagnosed with a drug-induced psychosis, one-third developed a schizophrenia-spectrum disorder within two years, and Caton and associates [81] found that one-quarter of early-phase psychosis patients diagnosed with substance-induced psychosis received a diagnosis of a primary psychotic disorder after just one year. Mathias and coworkers [82] noted that there exists a striking paucity of data on the outcome, treatment, and best practices for substance-induced psychotic disorders.

Of note, as discussed further below, clinical experience also suggests that heavy cannabis use among individuals with established psychotic disorders can be associated with short-term exacerbations of symptoms. Such observations are supported by results from a double-blind, randomized, placebo-controlled study of intravenous administration of Δ^9-THC in 13 stable, antipsychotic-treated patients with schizophrenia, which documented transient increases in cognitive deficits, perceptual aberrations, positive and negative symptoms, and motor disturbances [83]. Thus, even though individuals with psychosis might perceive an immediate benefit of cannabis use (e.g., euphoric and anxiolytic effects), worsening of diverse symptom domains is likely.

Cannabis Use and Misuse among Individuals with Schizophrenia-Spectrum Disorders

Broadly Defined Substance Abuse and Dependence in the Context of Schizophrenia-Spectrum Disorders

It is widely recognized that the prevalence of nicotine, alcohol, and illicit drug use and misuse is elevated among individuals with schizophrenia-spectrum disorders. Cannabis is the most common drug of choice. For instance, cannabis was used by 88% of hospitalized first-episode psychosis patients who had used drugs in a sample from Atlanta, Georgia, US, followed by alcohol, hallucinogens, and cocaine [84]. A similar distribution of drug use was found in an Italian sample of individuals with schizophrenia in which, among the 43% who reported using illicit substances, all had used cannabis, followed by hallucinogens (19%), stimulants (17%), and opiates (8%) [85]. Similar trends were also evident in an Indian sample; again, cannabis was the most commonly used substance, followed by alcohol [86]. Comorbid substance abuse and dependence among individuals with schizophrenia-spectrum disorders are associated with higher rates of relapse, a greater severity of positive symptoms [87–91], depression, interpersonal conflict [92], an increased risk of and shorter time to relapse, and an increased likelihood of inpatient admission [93, 94]. Furthermore, these associations are evident already at the time of the first episode [95].

Prevalence of and Motivations for Cannabis Misuse Among Individuals with Schizophrenia-Spectrum Disorders

An extensive literature review of worldwide epidemiological and clinical study samples estimated the 12-month and lifetime prevalences of cannabis use among individuals with psychosis to be 29.9 and 42.1%, respectively, with rates of cannabis misuse at 18.8% (12-month) and 22.5% (lifetime) [96]. While the literature is biased by reports from clinical samples, these rates are six or more times higher than those reported from the general population [12]. This high prevalence of cannabis use

has sparked interest in whether this represents an attempt to "self-medicate" among individuals with psychotic disorders. However, reported reasons for using cannabis in samples of individuals with schizophrenia and related disorders have not entirely supported this theory. For instance, in an Australian study on motivations for using cannabis, individuals with schizophrenia reported that boredom, social needs, poor sleep, anxiety and agitation, negative symptoms, and depression were the most important motivators of cannabis use [97]. A systematic literature review found that in diverse samples, individuals with schizophrenia most commonly report that their motivation is to enhance positive affect, relieve dysphoria, and facilitate social engagement [98] – motivations common to the general population – rather than to "self-medicate" specific psychotic symptoms. Furthermore, cannabis and other substance use is already highly prevalent among first-episode samples and retrospective studies document that the onset of cannabis use typically precedes the development of overt symptoms of schizophrenia [99].

Clinical Consequences of Cannabis Misuse Among Individuals with Schizophrenia-Spectrum Disorders

The effects of cannabis misuse on clinical features of individuals with schizophrenia are varied, including both transient and lasting effects, in domains such as age at onset of symptoms, symptomatology, neurocognitive performance, psychosocial functioning, and long-term course and outcomes. These adverse consequences of cannabis use disorder comorbidities may be driven by detectable neuropathological changes [100, 101]. For example, Rais et al. [101] conducted a study in which magnetic resonance imaging scans were obtained in 51 patients with recent-onset schizophrenia and 31 healthy controls. As expected based on prior research, gray matter volume loss over the 5-year study period was greater in patients with schizophrenia; however, the 19 patients who used cannabis (but no other drugs) during this 5-year interval lost gray matter at nearly twice the rate of the 32 patients who had not used the drug since the baseline scan. Further research is required to elucidate the specific CNS mechanisms by which cannabis use is associated with the clinical consequence discussed briefly below.

Effects on Positive and Negative Symptoms

While the literature is mixed, most evidence suggests that cannabis use is associated with greater levels of positive symptoms [94, 102, 103], though some have failed to replicate this effect [104]. In a double-blind, experimental setting, Δ^9-THC was found to transiently increase positive symptoms in a sample of individuals with schizophrenia [83]. In a South African sample, frequent cannabis use was associated with increased hallucinations, delusions, thought disorder, and bizarre behaviors [105]. First-episode patients have reported increased auditory and visual hallucinations, and confusion; some patients also recount experiencing their particular

psychotic symptom during cannabis intoxication. However, other data suggest that positive symptoms do not differ according to cannabis use when other substances are also taken into account [106]; or that patients with schizophrenia with and without comorbid cannabis use, who are treated with atypical antipsychotic agents, do not differ in positive and negative symptom scores [107]. Bersani and colleagues [85] found that cannabis users in an Italian sample had lower rates of thought disorder, though this may be confounded by patients' ability to obtain the substance, which is undoubtedly partly dependent on intact cognitive and social functioning. Furthermore, while this group found that hallucinations were greater among those individuals who began using cannabis before the onset of schizophrenia, this association was not present when the comparison included those who initiated cannabis use after the onset of the illness.

There is less evidence to suggest that cannabis use exacerbates negative symptoms. D'Souza and associates [83] found that in the aforementioned double-blind, experimental setting with individuals with schizophrenia, administration of Δ^9-THC resulted in a temporary increase in negative symptoms, such that participants appeared more blunted, less talkative, less spontaneous, and more internally preoccupied while under the influence of the substance. In a South African sample, increased avolition and apathy was observed among frequent cannabis users [105]. However, a number of studies have found that, even when adjusting for the effects of other drugs, lower, not higher, negative symptom scores are found in patients who use cannabis [85, 106]. Among first-episode patients in particular, those meeting criteria for comorbid cannabis dependence presented with significantly lower negative symptom scores at the time of first hospital admission [108]. The potential association between cannabis use and the absence of prominent negative symptoms is likely complex, as discussed previously [109]. Greater negative symptoms may impede social interactions necessary to initiate and maintain illegal drug use [110]. Because cannabis use is illegal in many countries, this substance is probably often more difficult to procure than alcohol, and individuals with prominent negative symptoms such as avolition, social isolation, and withdrawal likely would have some difficulty obtaining it [111]. Additionally, negative symptoms such as amotivation and anhedonia, may diminish the rewarding properties of drugs [112], making cannabis use less appealing to those with prominent negative symptoms.

Cannabis intake may exacerbate affective and other types of symptoms beyond the positive and negative domains. There have been mixed reports about the impact of cannabis use on depressed mood among individuals with schizophrenia-spectrum disorders [86, 92]. Comorbid cannabis use disorders were associated with suicide attempts in a French sample of schizophrenia patients [113]. Furthermore, when compared with controls, both putatively prodromal adolescents and first-episode patients reported feeling more anxious and depressed during periods of cannabis use, with long-term effects including depression, less control over thoughts, and social problems [114]. In the double-blind experiment with individuals with schizophrenia, administration of Δ^9-THC resulted in transient but clinically significant increases in a variety of symptoms, including somatic concerns, feelings of guilt, tension, uncooperativeness, unusual thought content, poor attention, and

preoccupation [83]. Additionally, an increase in perceptual alterations was observed, such that after consuming cannabis, participants appeared more "spaced out," and were more likely to behave in an unusual way or need redirection [83].

Effects on Neurocognition

The literature on cannabis use and cognition in the context of schizophrenia is mixed. Acute cannabis intoxication appears to cause cognitive impairment among individuals with schizophrenia, much like in the general population. In the double-blind experiment conducted by D'Souza and coworkers [83], participants with schizophrenia exhibited increased impairments in verbal learning, but not in verbal fluency, following administration of Δ^9-THC. However, in terms of long-term cognition, the association appears to be entirely reversed by some accounts. In a recent sample, patients with a comorbid cannabis use disorder demonstrated significantly better performance on measures of processing speed, verbal fluency, and verbal learning and memory [104]. A recent literature review found that, of 23 available studies in schizophrenia, 14 reported that cannabis users had better cognitive functioning than non-users, eight studies reported no or minimal differences in the two groups, and one study reported poorer cognitive functioning among the cannabis-using group [115]. A recent first-episode study found a few specific deficits among cannabis users, but greater generalized cognitive deficits among non-users [116]. This seemingly paradoxical finding could be explained by the aforementioned idea that cognitive abilities either directly or indirectly enhance individuals' ability to obtain illicit substances.

Effects on the Age at Onset and Mode of Onset of Psychosis

Regarding age at onset of psychosis, while most studies to date have reported differences between drug users and non-users without reference to the specific substances used, several have tested for an association between cannabis use specifically and the age at onset of psychotic symptoms. As reviewed by Compton & Ramsay [99], several studies have found that cannabis users/misusers had an earlier age at onset of psychosis than non-users [88, 89, 103, 117]. Recently, this was replicated in a South African sample [105]. Furthermore, González-Pinto et al. [118] extended this finding by demonstrating that cannabis use, abuse, and dependence were associated with a 7-, 8.5-, and 12-year decrease in the age at onset of psychosis, though the sample included patients with both nonaffective and affective psychoses. Compton and colleagues [7], in the US, found that an early progression to frequent premorbid cannabis use was associated with earlier ages at onset of prodromal symptoms and psychotic symptoms. By contrast, in a sample of 125 men with schizophrenia, those who had used cannabis did not have a significantly younger age at onset of symptoms than non-users [85]. Recently, Sevy and associates [119] found that compared to non-substance-abusing first-episode patients, those with a cannabis use disorder had an earlier age at onset of positive symptoms, though this association did not

persist when controlling for several other demographic and clinical variables, such as gender and premorbid adjustment.

Aside from age at onset of psychosis, there is also some evidence that the mode of onset of psychosis – how rapidly frank psychotic symptoms evolve – may differ in psychoses with comorbid cannabis use compared to those developing in the absence of cannabis use. Specifically, a more acute mode of onset has been noted among individuals with a psychotic disorder in the context of cannabis use [120, 121] (Compton MT, Broussard B, Ramsay CE, Stewart T, submitted for publication).

Effects on Long-Term Course and Outcomes

Numerous studies indicate that comorbid cannabis use, like the use of other illicit drugs, is associated with a poorer course of illness, including a greater number of relapses and hospitalizations. For instance, among outpatients in the Netherlands, those who reported using cannabis had their first relapse sooner and a greater number of relapses over the course of a year [122]. Similarly, in a South African study, those who used cannabis >20 times per year had a greater number of relapses and hospitalizations than those who did not [105]. By contrast, comorbid cannabis abuse or dependence was not associated with a greater number of hospitalizations or increased medication dosages in a French study [113]. Nonetheless, a systematic literature review found that cannabis use is quite consistently associated with increased risk of relapse and medication nonadherence [123].

Cannabis Use as a Cause of Schizophrenia-Spectrum Disorders: The Ongoing Debate

Studies Implicating Cannabis Use in Adolescence as a Component Cause

Several large-scale epidemiological studies lend credence to the assertion that cannabis use may be a "component cause" of schizophrenia. In a sentinel study involving over 50,000 Swedish conscripts, Andréasson and coworkers [124] found a dose-response relationship between cannabis use at conscription (at the age of 18 years) and schizophrenia diagnoses some 15 years later. Nearly two decades later, a follow-up of the same study showed that cannabis users were more likely than nonusers to be diagnosed with schizophrenia some 27 years later, even when controlling for a number of potential confounding variables [123].

In the Netherlands, a study of more than 4,000 individuals in the general population found that those using cannabis at baseline were nearly three times more likely to manifest psychotic symptoms at 3-year follow-up compared to individuals not using the drug, even after controlling for several potential confounders [125]. An apparent dose-response relationship was also observed. In a general population birth cohort of over 1,000 individuals in New Zealand, those using cannabis at the ages of

15 and 18 had higher rates of psychotic symptoms at age 26 compared to non-users, and the effect was stronger for earlier use [126]. In terms of specificity, the risk was specific to cannabis use as opposed to use of other drugs, and early cannabis use did not predict later depression. In a prospective birth cohort of nearly 4,000 individuals in Australia, McGrath et al. [127] found that early initiation of cannabis use (before about 15 years of age) was associated with an increased risk of nonaffective psychosis, scoring in the highest quartile of the Peters et al. [128] Delusions Inventory, and the presence of delusions. Furthermore, this association persisted when assessed among sibling pairs, thereby reducing the likelihood that the association was driven by residual confounding due to unmeasured shared genetic and/or environmental influences. Although a number of important limitations of such studies have been pointed out [129], the epidemiological evidence generally supports cannabis use as a component cause of schizophrenia and related psychotic disorders.

Given the accumulating literature, Arseneault and colleagues [4] reviewed five studies that included well defined samples drawn from population-based registers or cohorts and controlled for diverse potential confounders [3, 124–126, 130], and computed a pooled OR of 2.3 (95% confidence interval (CI), 1.7–2.9). Also in 2004, Smit and associates [5] reviewed five population-based, longitudinal studies (four of which were included in the aforementioned review) [3, 125, 126, 130, 131] in order to address five hypotheses about the relationship between cannabis use and schizophrenia: the self-medication hypothesis, the co-occurring drug use hypothesis, the confounding hypothesis, the interaction hypothesis, and the etiological hypothesis. They concluded that the first two could be eliminated, that more research is needed to rule out potential confounding effects, and that the latter two hypotheses (cannabis use increases risk but particularly in vulnerable individuals, and cannabis use makes its own unique contribution to the risk for schizophrenia) were both partly supported by the studies they reviewed. Weiser and Noy [44] pointed out that an alternative explanation is that pathology of the cannabinoid system in patients with schizophrenia may be associated with both increased rates of cannabis use and an increased risk for schizophrenia, without cannabis being a causal factor for schizophrenia.

A systematic review of 11 studies examining the relationship between cannabis use and psychosis (among which seven were included in a meta-analysis) found a pooled OR of 2.9 (95% CI: 2.4–3.6), suggesting that cannabis use is an independent risk factor both for psychosis per se and the development of psychotic symptoms in non-clinical samples [6]. Two years later, a systematic review of 35 studies revealed an increased risk of any psychotic outcome (independent of transient intoxication effects) in individuals who had ever used cannabis, with a pooled adjusted OR of 1.4 (95% confidence interval, 1.2–1.6), and results were consistent with a dose-response effect [132]. Given these large studies, reviews, and meta-analyses, there have been increasingly confident assertions in the field that cannabis use is a component cause; however, a number of limitations in the diverse studies conducted to date must be recognized. These include the diversity of operationalizations of psychosis outcomes, the fact that measures of cannabis use are usually based on self-report and not complemented by objective biological assays, potential confounding by the

effects of other concurrently used drugs, and difficulty in ruling out the possibility that prodromal manifestations of schizophrenia precede cannabis use [4, 133].

The apparent "causal" effect that is suggested by the replicated association could have three different directionalities. Cannabis use may cause psychosis, or in those individuals with underlying vulnerabilities in particular. Alternatively, psychosis may make individuals more likely to use cannabis. Finally, a shared diathesis may underlie both outcomes. The first theory – increasingly viewed as a likely explanation – is explored in more depth below through a consideration of criteria for establishing causality. Potential evidence for the second and third theory is given below under "coherence and consideration of alternative explanations."

Criteria for Establishing Causality

Published in 1965, Austin Bradford Hill's criteria for establishing a causal effect have been used widely in epidemiological inquiries [134]. These criteria are often used as a checklist for establishing causality, though Hill himself did not intend them to be used in this way [134]. Hofler [134] provides a thorough description of Hill's criteria and their application in current research. Arseneault and coworkers [129] outlined an extensive review of the definitions of a cause in relation to cannabis use potentially causing schizophrenia, as well as an exposition of three key criteria for establishing causality: *association* (the cause and the disease appear together), *temporal priority* (the putative cause is present before the disease), and *direction* (changes in the putative cause lead to changes in the outcome, as opposed to being driven by a confounding third variable). In the sections that follow, Hill's criteria, along with a brief summary of each in relation to the link between cannabis use and psychosis, are given.

Strength

A strong association is more likely to have a causal component than is a modest association. Cannabis use has a relatively weak but consistent association with psychotic disorders, on a similar scale to other known single environmental risk factors. Perhaps the most compelling reason to consider cannabis as a potential cause of schizophrenia is that multiple prospective studies have found cannabis use to be associated with a greater odds of developing psychosis, as discussed above. A review of seven prospective studies noted that this effect persisted after the studies controlled for various potential confounding factors such as intelligence, psychiatric symptoms at baseline, and sociodemographic variables [135]. While this effect is replicated in longitudinal studies, it is arguably relatively weak compared to the causal risk factors implicated in some other human health conditions. Yet, other well established environmental risk factors for schizophrenia have similar effect sizes, including obstetric complications during birth (OR: 2.0, CI: 1.6–2.4) [136], and a history of sexual abuse (adjusted OR: 2.9, CI: 1.3–6.4) [137]. Therefore, cannabis use is plausible as one of many component causes that, in concert, may result in

the development of schizophrenia-spectrum disorders. Though it may be a relatively small added risk for individuals who are not otherwise vulnerable, cannabis consumption is widely prevalent in the general population and could therefore be implicated in a fairly large number of cases.

Consistency

A relationship is observed repeatedly. Although the variation of psychosis-related outcomes that have been examined in relation to cannabis use may be seen as a methodological limitation across the body of extant studies, it also provides for a confirmation of consistency of the observed association. In addition to being associated with schizophrenia, more broadly defined psychotic disorders, and psychotic symptoms, cannabis use has also been associated with greater schizotypy among undergraduate college students [138–141] as well as symptoms consistent with the prodrome among adolescents [142].

Specificity

A factor influences specifically a particular outcome or population. Arseneault et al. [4, 129] pointed out several studies that indicate both specificity of the exposure (cannabis use as opposed to use of other drugs) and specificity of the outcome (schizophrenia and other psychosis-related outcomes as opposed to other domains of psychiatric disorders). However, further research is clearly needed regarding both aspects of specificity. As noted above, a number of psychosis-related outcomes have been examined, as opposed to a single, specific outcome (e.g., hallucinations). Furthermore, given the variability in active constituents of ingested cannabis, along with differences in their biological effects, research will need to further disentangle the causal influences of specific compounds.

Temporality

The factor must precede the outcome it is assumed to affect. In most studies that have examined the temporal sequencing of cannabis use and psychosis, first-episode patients report initiating cannabis use before the onset of psychotic symptoms, oftentimes by several years [85, 99]. Several studies have found that the majority of individuals with a recent-onset psychosis report initiating use even before the first sign of the prodrome [7, 99]. If cannabis use is typically initiated or increased after the onset of schizophrenia, it may be considered a consequence of the disorder, rather than a cause of it. This would fit better into the argument that individuals with schizophrenia-spectrum disorders use cannabis to "self-medicate" or reduce particular symptoms that are distressing [88].

One complicating factor is that in order to determine a temporal association, the onset of schizophrenia must be defined. The most obvious point of reference may be the onset of positive symptoms such as delusions, hallucinations, or disorganization. However, some would argue that the onset of the prodrome may be

a more valid reference point for studies of causality, as this represents a period of distinct changes that are later recognized as the early signs of an emerging disorder. Furthermore, premorbid deficits are widely recognized, and a retrospective study using home videos found increased neuromotor abnormalities in children as compared to their siblings, starting as early as infancy [143]. These findings, along with evidence that pregnancy and birth complications, season of birth, and early developmental delays are risk factors for developing schizophrenia [144], suggest that the later development of the disorder could be related to genetic and environmental vulnerabilities that have existed from birth. These factors make a determination of temporality an ongoing challenge.

Biological Gradient

The outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory. Larger doses or longer exposure to cannabis – especially in early adolescence – appear to be associated with a higher risk of psychosis and a hastened onset of psychosis. Most studies to date compare patients in dichotomized groups, either by the presence or absence of cannabis use beyond a certain threshold or by the presence or absence of a cannabis use disorder. However, in a prospective study, Henquet and colleagues [145] found a dose-response relationship between cannabis use and psychotic outcomes, with ORs of developing psychosis progressively increasing with frequency of use, ranging from 1.0 (CI: 0.5–1.9) among those using cannabis once a month or less, to 2.6 (CI: 1.5–4.3) among daily users. As noted previously, González-Pinto and associates [118] documented a decrease in age at onset of psychosis (nonaffective or affective) of 7, 8.5, and 12 years, respectively, in individuals with cannabis use, abuse, and dependence, when compared with non-users.

Biological Plausibility

The observed association can be plausibly explained by substantive (e.g., biological) explanations. As outlined elsewhere [45, 83], there are several possible mechanisms by which Δ^9-THC might increase or cause de novo positive, negative, and cognitive symptoms of schizophrenia. For example, the effect of cannabinoids on increasing mesolimbic dopaminergic activity may explain the fact that positive symptoms can be induced by Δ^9-THC in controlled pharmacological studies [45]. In terms of specific phenotypes (or endophenotypes), the administration of Δ^9-THC in healthy volunteers results in an impairment in visual information processing that is similar to impairments observed in individuals with schizophrenia or those who are at high risk of developing the disorder [146]. As noted in the above brief overview of the endocannabinoid system, researchers are avidly studying a number of aspects of the endocannabinoid ligands, the CB_1 receptor, and genetic polymorphisms that could further elucidate the biological plausibility of the link between cannabis and psychosis. Several useful reviews of the potential neuropsychological and biological plausibility of the cannabis–psychosis link – a topic beyond the purview of this chapter – are available in the recent literature [67, 147–152].

Experiment

Causation is more likely if evidence is based on randomized experiments. As previously suggested, experimental administration of Δ^9-THC supports the notion that this agent induces diverse experiences similar to those observed in schizophrenia. Furthermore, emerging experimental evidence from animal and human studies indicates that CB_1 receptor antagonists (including rimonabant and CBD) may exert antipsychotic effects. Ongoing research may find further experimental, rather than observational, support for cannabis use as component cause of schizophrenia-spectrum disorders.

Analogy/Coherence with Existing Theory and Knowledge

For analogous exposures and outcomes, an effect has already been shown. The fact that an environmental exposure may cause psychiatric symptoms or disorders is not a novel concept, and that such effects may be more likely among individuals already predisposed to the psychiatric disorder is not surprising. Thus, the increasingly agreed upon notion that cannabis consumption during a critical period of brain development [153, 154] could serve as a component cause of later psychiatric illness through effects on key neurobiological systems is coherent with both the widely accepted neurodevelopmental theory and diathesis-stress model of schizophrenia. Diverse environmental risk factors, ranging from apparently sufficient causes (e.g., *Treponema pallidum* causing the general paresis stage of neurosyphilis) to other presumed component causes (e.g., obstetric complications) are known to be associated with the onset of psychosis, and exposure to a psychoactive ingested drug is analogous to such risk factors in modern conceptions of complex disease causation.

Coherence and Consideration of Alternate Explanations

A causal conclusion should not fundamentally contradict present substantive knowledge. While substantial evidence supports the theory that cannabis may have a causal effect in schizophrenia, not all research supports this notion, and other plausible theories have been proposed to explain the association. A valid concern was raised by Degenhardt and coworkers [155], who found that the incidence of schizophrenia – and the age at onset of incident cases – in Australia did not change with trends in cannabis use, as would be expected using mathematical models. The data appeared to fit better with the hypothesis that cannabis use hastens the onset in those with pre-existing vulnerabilities or is associated with psychosis either through reverse causality or a shared diathesis.

Regarding reverse causality, the alternate explanation commonly put forth (in arguments that cannabis use is not a component cause of schizophrenia) is that psychosis may be a risk factor for cannabis use. Bersani et al. [85] proposed that cannabis consumption may represent an effort to "self-medicate" in some, particularly to reduce negative, rather than positive, symptoms. (Of note, Tucker [95] suggested that the "self-medication" terminology is misleading as drugs of abuse

are generally inappropriate as medications and they do not appear to be associated with effective treatment outcomes.) Henquet and colleagues [135] dispute this as an explanation for the association between cannabis and psychosis, noting that prospective studies find cannabis associated with the later development of psychosis, even when those individuals with early indicators of vulnerability are excluded.

As mentioned above, yet another compelling alternate explanation is that the connection between cannabis use and psychosis may be explained by a shared diathesis. A cohort study in the Netherlands found that cannabis use in youth predicted future psychotic symptoms, and that psychotic symptoms in those who had never previously used cannabis predicted future cannabis use [156]. Such findings might indicate a shared diathesis. Henquet and associates [145] found that the association with cannabis use is substantially greater among adolescents with previously established vulnerability to psychosis. However, in this prospective study, psychosis proneness in early adolescence did not predict the initiation of cannabis use. Thus, some, but not all, evidence suggests a bidirectional effect, which may be underpinned by a shared genetic diathesis for both cannabis use and psychosis.

The Balance of the Evidence: Cannabis Use Appears to Be a Component Cause

Taken together, the extant evidence suggests that premorbid cannabis use is a component cause of schizophrenia (rather than being a necessary cause or a sufficient cause), meaning that it probably contributes – in conjunction with other factors – to forming a complex causal constellation, along with other component causes, that leads to the disorder [4, 129, 133]. In general, the evidence suggests that cannabis use doubles the risk of developing schizophrenia in the long term [4]. However, as pointed out by McGrath and coworkers [127], the relationship is probably not strictly unidirectional; individuals who are vulnerable to developing psychotic disorders may be more likely to initiate cannabis use, which could then subsequently contribute to an increased risk of disorder.

One of many unanswered questions pertains to why only a small portion of individuals using cannabis develop psychotic symptoms or schizophrenia [133]. Most importantly, cannabis use is conceptualized as a component cause, rather than a sufficient cause. Thus, cannabis use may act in conjunction with genetic susceptibilities or with other environmental risk factors. The former is exemplified by the hallmark finding of Caspi et al. [157] that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis; specifically, carriers of the valine allele were most likely to develop psychotic symptoms and to develop schizophreniform disorder if they had used cannabis, but cannabis use had no such adverse influence on those with two copies of the methionine allele. Of note, recent evidence

suggests that this same gene-environment interaction may be associated with the age at onset of psychosis among first-episode patients [158]. Regarding potential interactions with other environmental risk factors, Harley and colleagues [159] reported that, in a sample of 211 adolescents between 12 and 15 years of age, both cannabis use and childhood traumatic experiences were significantly associated with the risk of experiencing psychotic symptoms; however, the presence of both early cannabis use and childhood trauma increased the risk beyond that posed by either risk factor alone, indicating a greater-than-additive interaction.

Of note, a major limitation to the ability of researchers to address the debate on cannabis use as a potential causal factor in schizophrenia-spectrum disorders is the widely recognized phenomenologic, and likely etiologic, heterogeneity of these disorders. Without valid groupings of patients into etiologically homogenous subsets, studies designed to elucidate causal associations are made more difficult.

Treatment and Prevention Implications Pertaining to the Interface of Cannabis Misuse and Schizophrenia-Spectrum Disorders

Treatment Implications

In general community samples of individuals with cannabis use disorders, cognitive-behavioral therapies and motivational interviewing techniques have proven beneficial [160, 161]. There is also some evidence for the effectiveness of contingency management (e.g., providing monetary-based reinforcement contingent on documented abstinence). Research on pharmacological approaches is nascent [161]. In general, the evidence base on the management of cannabis abuse and dependence in the general population is largely lacking, and the same is true of such treatments specifically among individuals with schizophrenia-spectrum disorders. Freedman [162] noted that the cumulative data suggest that cannabis use conveys long-term adverse consequences, and that patients with psychotic disorders and their families therefore need to understand these negative effects and be encouraged to engage in treatment for cannabis abuse and dependence.

The high rates of cannabis and other drug use among those with psychotic disorders suggests that all such patients should be screened, and those with a substance abuse or dependence diagnosis should be offered integrated treatment (as opposed to sequential or parallel treatments for the dual diagnoses) [163]. James and Castle [164] reviewed approaches to screening, assessing, and treating cannabis abuse and dependence in people with psychotic disorders. They note that as part of the detailed assessment process, the nature and degree of drug use, impact on illness, reasons for use, past treatments, and motivations to change should be considered. In addition to cognitive-behavioral therapies and motivational interviewing techniques, elements of the 12-step philosophy, psychoeducation, harm reduction, skills training, and

relapse prevention have also been used [164]. Several recent reports have reviewed the literature on the treatment of cannabis misuse among people with psychotic disorders [165, 166].

Given that cannabis misuse commonly begins and escalates during adolescence and young adulthood, particular attention must be given to cannabis abuse and dependence among individuals with first-episode or early-course psychotic disorders. As noted above, the rates of cannabis misuse are high, and ages at initiation of use are early, among first-episode patients. For example, in Melbourne, Victoria, Australia, Hinton and associates [167] documented that 88.5% of 130 first-episode patients reported a lifetime history of cannabis use, and 73.8% were already regular users. Similarly, in Atlanta, Georgia, US, Stewart and coworkers [84] found that 79.8% of 109 first-episode patients had previously used cannabis, and that 60.6% had used it on a weekly or daily basis. In those two first-episode cohorts, the mean age of initiation of regular use was 16.7 and 16.5 years, respectively (with an earlier age of first use). These figures are of importance given that early initiation and regular use of cannabis in adolescence are known to be risk factors for later problematic cannabis and other drug use, lower educational attainment, criminal behavior, and other adverse consequences in general population samples [161]. Also as noted previously, use of cannabis in the context of schizophrenia-spectrum disorders, even among first-episode samples, is associated with poor medication adherence, greater severity of positive symptoms, and higher risk of relapse [168–170].

These and other findings point to a serious need for specialized cannabis misuse treatment services for first-episode patients. Yet, remarkably little is known about efficacious treatment approaches in this population. In a naturalistic study of a comprehensive, community-based, early intervention service, Hinton et al. [167] found a significant reduction in cannabis use during the initial few months of treatment, despite the fact that the service provided only educative feedback with respect to substance use (e.g., highlighting potential complications of continued use and recommending abstinence). The authors suggested that such indications of reductions in cannabis use during the early treatment of first-episode psychosis should engender optimism that readiness to change may be especially salient in the period following initial diagnosis. Other highly regarded specialized early intervention programs have described experiences with an integrated approach to reduce substance use in individuals experiencing a first episode of psychosis [171].

Given the dearth of specifically designed treatments for cannabis abuse and dependence for first-episode patients, existing approaches typically include components such as motivational enhancement, psychoeducation, skills training and support, and taking into account the stage of recovery [95]. In Australia, Edwards and colleagues [172] tested a cannabis-focused intervention (an individually delivered, cognitive-behavioral, harm-minimization approach involving 10 weekly sessions) in 23 first-episode patients compared to a psychoeducational control condition in 24 patients. They found that both conditions were associated with reductions in

cannabis use at the end of treatment and at 6-months post-intervention, suggesting that relatively simple interventions may be beneficial, but that further research is needed on specialized approaches.

Prevention Implications

In light of the fact that premorbid/adolescent cannabis use appears to be a component cause of schizophrenia-spectrum disorders, several authors have suggested prevention implications. Arseneault and associates [129] noted that although the majority of young people who use cannabis do so without serious consequences, a vulnerable minority will experience harmful outcomes, and that cannabis use among psychologically vulnerable young adolescents should be strongly discouraged by parents, teachers, and health professionals. Furthermore, they note that policy-makers should concentrate on public health measures to delay the initiation of cannabis use given that the youngest cannabis users appear to be most at risk. In their systematic review, Moore and coworkers [132] suggested that there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life. In doing so, they noted that even though one's individual lifetime risk of a psychotic disorder – even among those who use cannabis regularly – is likely to be low, cannabis use probably has a substantial effect on psychotic disorders at the population level because exposure to the drug is so common.

As pointed out previously [7], in light of the rapid growth in research that aims to prospectively identify samples in an ultra-high risk state, or potentially prodromal syndrome, indicated preventive interventions using both psychopharmacologic (e.g., low-dose atypical antipsychotic agents) and psychotherapeutic (e.g., cognitive-behavioral therapy) modalities could benefit from also testing whether the prevention and treatment of cannabis use would delay conversion to a psychotic disorder. The possibility of delaying onset of psychosis, by reducing premorbid or prodromal cannabis use among those at high genetic or psychometric risk, could result in substantial improvements in outcomes (in addition to ameliorating problems associated with cannabis use disorders once a psychotic disorder is clearly present). Although data on cannabis use among ultra-high risk or potentially prodromal samples is very limited, one study involving 48 such individuals found that at 1-year follow-up, only one of 32 subjects who had no or minimal cannabis use had converted to psychosis (3.1%), compared to five of 16 (31.3%) who met criteria for cannabis abuse or dependence [173]. Though very preliminary and in need of replication in larger samples, such results suggest that preventing or treating cannabis use in such individuals could delay, or perhaps even avert altogether, the onset of psychosis.

Despite these findings and a multitude of calls for preventive approaches, the evidence base pertaining to primary or secondary prevention of cannabis use disorders among individuals with latent or overt schizophrenia-spectrum disorders is

virtually nonexistent. Given the extent of the comorbidity, and the public health burden posed by cannabis and other drug misuse, focused development and research is clearly needed.

Conclusions and Future Directions

The world's most commonly abused illicit substance appears to have a number of unique associations with schizophrenia-spectrum disorders. This chapter has provided an overview of some of the key aspects of the interface: both exogenous and endogenous hypotheses have been put forth concerning the role of cannabis and the endocannabinoid system in schizophrenia; the potential for cannabis use to induce psychotic symptoms or syndromes has been long recognized; there are high rates of cannabis misuse among patients with first-episode and chronic psychotic disorders; such use is associated with diverse clinical consequences; and increasing evidence suggests a causal association between premorbid cannabis use and psychotic outcomes. A number of future directions for research are evident, only a few of which are mentioned here, in addition to many others that can be gleaned from the foregoing sections of this chapter.

First, given the fact that ingested cannabis contains varying levels of diverse constituents, and that some of these may have opposing effects (e.g., Δ^9-THC and CBD, which appear to have psychotomimetic and antipsychotic properties, respectively), it is crucial for the field to further examine the effects of specific phytocannabinoids. For example, in the first study of its kind, Morgan and Curran [17] found that individuals with evidence of Δ^9-THC only in their hair samples had higher rates of unusual experiences (a dimension of psychosis-proneness that may be considered an analogue of hallucinations and delusions) compared to those with no cannabinoids or a combination of both Δ^9-THC and CBD in their hair samples. Such findings clearly have important implications for research into the link between cannabis use and psychosis.

Second, continued research on the endocannabinoid system, and on naturally occurring or synthetic agents that interact with this system, will undoubtedly lead to advances in the field's understanding of the complex link between cannabis use and psychotic disorders. As demonstrated by early studies of rimonabant, such agents may hold promise for the treatment of psychotic disorders, other psychiatric disorders, and general medical conditions. Third, although cannabis use, especially in early adolescence, is now generally considered to be a component cause of schizophrenia-spectrum disorders, further research is warranted on the other potential direction of causality (i.e., psychotic and other types of symptoms leading to initiation or escalation of cannabis use) and on the bidirectional and shared diathesis hypotheses. Another area for future research pertains to the great need to develop more effective interventions for the treatment – and ultimately primary prevention – of cannabis use disorders, especially among those with, or predisposed to, schizophrenia and related psychotic disorders.

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Chapter 15
Schizophrenia and Comorbid Substance Abuse – Pathophysiological and Therapeutic Approaches

Thomas Wobrock, Dirk Czesnik, and Berend Malchow

Abstract Substance use disorder is the most common psychiatric comorbidity in schizophrenic patients, with prevalence rates of up to 65%. Besides the legal substances tobacco and alcohol, cannabis seems to be the most illicit drug abused in schizophrenia patients and has been discussed as an important risk factor for developing schizophrenia. At least substance abuse may contribute to an earlier onset of schizophrenia as seen in many first-episode studies. Common hypothetic models for the increased comorbidity include the concept of increased vulnerability to each individual disorder, the model of a secondary substance use or psychotic disorder, and the bidirectional model. There is no common sense regarding a different neurobiological background for schizophrenia patients with and without substance abuse. Previous substance abuse (primarily cannabis) seems not to lead to pronounced structural brain abnormalities in schizophrenia, but may cause functional changes on cortical inhibition processes and synaptic transmission involving mainly the GABAegic, glutamatergic and dopaminergic system. The key issue in providing treatment for this population is developing a dual disorder approach that integrates treatment of substance abuse and schizophrenia. Many programmes are now providing this integration through interdisciplinary teams with expertise in the treatment of schizophrenia and substance abuse. This form of treatment features assertive outreach, case management, family interventions, housing, rehabilitation and pharmacotherapy. It also includes a stagewise motivational approach for patients who do not recognize the need for treatment of substance use disorders and behavioural interventions for those who are trying to attain or maintain abstinence. Nevertheless, that the evaluation of combined treatment programs with motivational elements, psychoeducation and cognitive-behavioural approaches shows an effect in reducing substance abuse and in decreasing frequency and severity of psychotic decompensations, there is only a slight advantage over routine care. Pharmacotherapy of patients with the dual diagnosis of a schizophrenia and comorbid substance use disorder is

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a highly challenging topic because this subgroup of patients shows a high relapse rate, low treatment adherence and high rate of side effects. Recommendations for antipsychotic pharmacotherapy in schizophrenia are mainly based on studies that excluded patients with this dual diagnosis. The preferred pharmacological strategy depends on the target symptoms: improvement of schizophrenic psychopathology, reduction of craving and substance use, treatment of concomitant symptoms like depressive mood or management of side effects. Data, mainly based on open studies or case series, suggest superior efficacy for second generation antipsychotics (SGAs) over conventional antipsychotics (FGAs) with regard to improvement of the above mentioned target symptoms. Antidepressants and anti-craving agents (naltrexone) given adjunctive to antipsychotic maintenance therapy showed efficacy in reducing substance use and craving. In conclusion, there is an increasing need to proceed researching the pathophysiological background of this comorbidity to develop new treatment approaches. The insight into the pathomechanisms of the endocannabinoid system may help to find innovative treatment strategies in schizophrenia without substance abuse.

Keywords Schizophrenia · Comorbid substance abuse · Cannabis · Antipsychotics · Psychological interventions

Abbreviations

2-AG	2-arachidonoylglycerol
ACC	Anterior cingulated gyrus
ACT	Assertive community treatment
AEA	Anandamide
BDNF	Brain derived neurotrophic factor
CB1	Cannabinoid receptor 1
CBD	Cannabidiol
CBT	Cognitive behavioural therapy
CM	Case management
CNR1	Cannabinoid receptor 1 gene
COMT	Catechol-O-methyltransferase
CSF	Cerebro-spinal fluid
D2-receptor	Dopamine-2-receptor
delta-9-THC	Delta-9-tetrahydrocannabinol
DRT	Dual recovery therapy
eCS	Endogenous cannabinoid system
EPS	Extra-pyramidal symptoms
ERP	Event-related potentials
FAAH	Fatty acid amide hydrolase
FGA	First-generation antipsychotics
GABA	Gamma amino butyric acid
ICF	Intracranial facilitation
MAO	Monoaminooxidase

MET	Modified motivational enhancement therapy
MI	Motivational interviewing
MMN	Mismatch negativity
MRI	Magnetic resonance imaging
NMDA	N-methyl D-aspartate
NRG1	Neuregulin 1 gene
PANSS	Positive and negative symptome scale
PFC	Prefrontal cortex
RCT	Randomised controlled trial
ROI	Region of interest
SAMM	Substance abuse management module
SGA	Second-generation antipsychotics
SICI	Short interval cortical inhibition
Smri	Structural magnetic resonance imaging
ST	Skills training
STG	Superior temporal gyrus
SUD	Substance use disorder
TMS	Transcranial magnetic stimulation

Introduction

Schizophrenia is a major psychotic disorder that usually appears in late adolescence or early adulthood and has a lifetime prevalence of 1%. Despite modern treatment techniques, schizophrenia still presents an enormous burden to the patients and their relatives. Substance abuse in individuals with schizophrenia is very common; it has become the most prevalent comorbid psychiatric condition associated with schizophrenia and contributes to an unfavourable disease course [1]. Besides the legal substances tobacco and alcohol, cannabis seems to be the most illicit drug abused in schizophrenia patients with rates of comorbidity ranging from approximately 15 to 65% [2, 3]. In a population-based study, the prevalence of substance use disorder in patients with schizophrenia was estimated to be 4.6 times higher than in the general population [4]. Substance abuse, especially cannabis has been discussed as an important risk factor for developing schizophrenia. At least substance abuse may contribute to an earlier onset of schizophrenia as seen in many first-episode studies.

Persisting comorbid substance use has been associated with negative outcome in schizophrenia, including more frequent and longer periods of hospitalization, higher relapse rates even in first-episode patients, elevated EPS rates, lower medication compliance, unemployment, violence, higher rate of criminality and greater risk of committing suicide [5–12]. Hypotheses explaining the possible aetiological relationship between the two disorders include concepts of common increased vulnerability to both disorders with regard to dysfunctional affect regulation or deficits with stress coping, of secondary substance abuse (in the context of self-medication

or increased sensitivity to drug effects), of secondary psychotic disorder triggered or induced by substance use and of a bidirectional maintenance of both disorders by neurobiological or psychological interaction [13, 14]. The effects of abused substances on schizophrenic symptoms vary, making it difficult to differentiate between substance-abuse-related symptoms and those related to functional psychosis [1]. For example, alcohol hallucinosis closely resembles paranoid schizophrenia [15].

Differences in psychopathology between schizophrenia patients with and without substance abuse were reported inconsistently in the recent literature. Comorbid substance abuse has been associated with higher positive symptomatology (e.g. [16–18]), lower negative symptoms (e.g. [17, 19, 20]), fewer positive and negative symptoms (e.g. [21]), and no significant differences at admission and follow-up [22].

Neurobiological Background and Pathophysiology

A number of epidemiological studies clearly show that cannabis abuse is associated with a greater risk of suffering from psychotic symptoms or from developing schizophrenia [23–28]. However, there is no common sense regarding a different neurobiological background for schizophrenia patients with and without substance abuse. Previous substance abuse (primarily cannabis) seems not to lead to pronounced structural brain abnormalities in schizophrenia [29], but may cause functional changes on cortical inhibition processes and synaptic transmission involving mainly the GABAegic, glutamatergic and dopaminergic system [30].

In the following section a short review about the findings concerning neurocognition, structural magnetic resonance imaging (sMRI), neurophysiology and genetics will be given.

Neurocognitive Function

Neurocognitive deficits have been recognised as an important feature, or even a core deficit, of schizophrenia (e.g. [31, 32]). A meta-analysis reviewing 204 studies looking at performance of patients with schizophrenia relative to healthy controls reported broad-based cognitive impairment with varying degrees in several cognitive domains, e.g. general intellectual function, global and selective verbal memory, nonverbal memory, visual and auditory attention, executive function, language, spatial ability, motor performance, and interhemispheric tactile transfer test performance [33]. Some of these deficits including reduced function in verbal memory and learning, visual memory, abstraction, cognitive flexibility, language abilities and attention have been found even in untreated, first-episode patients [34]. Cognitive functioning is a correlate of global and specific functional outcome in schizophrenia and contributes to poor judgement and lack of insight [35]. Cognitive impairments account for significant variance in measures of functional status [36].

Neurocognitive Function in Chronic Schizophrenia with Comorbid Substance Abuse

Substance abuse and dependence has been associated with deleterious consequences on cognitive function, mostly reported in patients consuming alcohol and cocaine [37, 38], but also found in patients with long-term cannabis abuse (e.g. [39]). Despite the high prevalence of comorbid SUD in schizophrenia there is still few knowledge about the influence of substance abuse on neurocognitive function in schizophrenic patients. Studies to date revealed inconclusive results [40]. Patients with chronic schizophrenia and with comorbid SUD (cocaine and alcohol consumers) presented greater cognitive deficits than patients without substance abuse (e.g. [41–44]), whereas other studies demonstrated no differences between users and nonusers or even better performance of patients with concomitant SUD (e.g. [40, 45–52]). A recent study demonstrated more impaired memory function in older schizophrenic patients with comorbid alcohol abuse [44]. Some studies indicated that cognitive impairment in drug abusers occurs after prolonged and excessive use (e.g. [49]).

One study found even better neuropsychological performance of patients with lifetime history of cannabis abuse in verbal and spatial recognition or recall [53], but differences of memory function were no longer significant after adjustment on covariables (e.g. age, gender, education). In contrast to these cognitive domains subjects with comorbid cannabis use disorder performed poorly on an interference task (Stroop-Test).

Neurocognitive Function in First-Episode Patients with Comorbid Substance Abuse

Only limited research has been conducted in assessing the effect of comorbid substance abuse in recent-onset schizophrenia or first-episode patients [22, 40]. In one study patients with recent-onset schizophrenia or schizoaffective disorder and comorbid substance abuse (SUD) showed no significant differences in a wide range of cognitive domains including verbal fluency, visual-spatial ability and motor speed, short-term memory and early information processing, attention, and executive functioning and cognitive flexibility [22]. Another study examining the impact of substance abuse, particular alcohol and cannabis, on neurocognitive function in a sample of first-episode patients revealed no significant associations with substance abuse [40]. Considering the younger age, shorter illness duration and fewer amount of lifespan drug intake in patients with recent-onset schizophrenia compared to subjects with chronic disease, it is possible that the effects of substance use on cognitive impairment are not yet evident.

In summary, most studies did not find an additional cognitive impairment in individuals with schizophrenia who use substances, especially focusing on alcohol and cannabis abuse (e.g. [22, 40, 45–47]).

Brain Morphology and Neuroimaging

Volumetric sMRI Studies in Schizophrenia

Brain abnormalities identified in schizophrenia using neuroimaging techniques reveal evidence for structural and functional impairment in multiple brain regions focusing on frontal cortex, temporal cortex, thalamus, hippocampal complex, basal ganglia and even cerebellum [54]. Meta-analyses and reviews of published studies concerning volumetric measurements obtained by magnetic resonance imaging (MRI) (e.g. [55, 56]) have demonstrated ventricular enlargement and volume decrease especially of frontal and temporal lobe structures in schizophrenia [57]. A meta-analysis of volumetric structural MRI studies investigating hippocampus reported a 4% bilateral volume reduction in schizophrenic patients [58], while some studies observed pronounced decrease of hippocampal structure only on the left side (e.g. [59]). Abnormalities of temporal lobe structures linked to mesolimbic system were suggested as responsible for cognitive and emotional disturbance commonly seen in schizophrenia. Temporal volume reductions have been linked to clinical features [60]. Especially reduced bilateral hippocampal size has been associated with memory deficits, and the decrease of total volume of superior temporal gyrus (STG) correlates with the severity of thought disorder and auditory hallucinations [59, 61]. In first-episode and neuroleptika-naïve patients results of volumetric MRI studies are inconclusive [62]. Ventricular enlargement in neuroleptika-naive patients up to 20% compared to healthy controls was observed in most studies, but volume changes of cerebral structures are less conclusive. While most studies failed to detect a volume reduction in basal ganglia [62], a decreased thalamus volume was frequently reported (in the range of 5–18% of thalamus volume compared to controls) [63–65]. Additionally gray matter of frontal and temporal lobe structures, especially entorhinal cortex and hippocampus, was found reduced [60, 66, 67].

Volumetric sMRI Studies in Patients with Cannabis Abuse

The structural neuroimaging studies in cannabis abusers revealed conflicting results [68]. While two studies could not demonstrate an influence of cannabis on brain morphology, especially on hippocampus, compared to controls [69, 70], a third study found lower gray matter volumes in the right parahippocampal region, lower white matter density in the left parietal region as well as increased volumes of bilateral fusiform gyrus, right thalamus and left parahippocampal region in the group of chronic cannabis users [71]. Other investigators detected only less frontal white-matter volume percentage in the group of substance abusers (cannabis, opiates, cocaine) compared to healthy controls [72]. Another study without healthy control group revealed a significant correlation between age of first use and decreased total brain volume [73]. Subjects who started using marijuana before age 17, compared to those who started later, revealed smaller whole brain and percent cortical gray matter and larger percent white matter volumes [73].

Volumetric sMRI Studies in Schizophrenia with Comorbid Substance Abuse

There is still limited knowledge about the influence of substance abuse on brain morphology in schizophrenic patients.

A study examining brain volumes in cannabis-exposed patients with schizophrenia versus non-exposed patients with schizophrenia revealed no differences between the subgroups for total brain volume, total gray and white matter, ventricles, cerebellum and caudate except a decreased asymmetry of the lateral ventricles in the cannabis-exposed patients [74]. In a recent longitudinal study the same research group could demonstrate that first-episode schizophrenia patients with continued use of cannabis showed increased loss of cerebral gray matter volume and larger increases in lateral and third ventricle volumes than healthy subjects and patients who did not use cannabis during the follow-up [75]. Nevertheless, brain volumes of schizophrenia patients with and without cannabis abuse did not differ significantly at the beginning of the longitudinal study, although it has to be assumed that the patients abused cannabis several years before entering the study and the mean duration of schizophrenic illness is more than 1 year. Another study investigating the volumes of the superior frontal gyrus, anterior cingulated gyrus and orbital frontal lobe found less anterior cingulate gray matter in cannabis abusing first-episode schizophrenia patients compared with patients who did not abuse cannabis and healthy volunteers [76].

The association of reduced volume in anterior cingulate gyrus (ACC) and the history of cannabis abuse in schizophrenia was interpreted in the context of a disturbed function of ACC with the consequence of poor decision-making and more compulsive drive towards drug use as a predisposition for substance abuse and not as a toxic effect of cannabis itself.

This contrasts with a study finding no volumetric differences in the ACC, the amygdala-hippocampus complex, the superior temporal gyrus and the lateral ventricles between recent-onset schizophrenia patients with and without previous cannabis abuse [77]. In this study the patients without previous cannabis abuse tended to demonstrate more reversed temporal asymmetry as the non-users. This may be a subtle hint that the subgroup of cannabis abusers lower their threshold for psychosis through drug abuse itself and the other subgroup increases the vulnerability by presenting slightly more brain abnormalities.

Although no data regarding the amount of cannabis consumption was given in most studies, one could speculate if differences in substance use are responsible for the conflicting results. In addition, the heterogeneity of the definition of the regional volume (ROIs) boundaries, differences in MRI techniques and volume extractions in previous studies make it difficult to compare volumetric measurements. Decreases of gray and white matter volume over time may also be related to the duration, type and cumulative dose of antipsychotic medication patients received.

In summary, there is some evidence that chronic cannabis abuse could alter brain morphology, but there is no evidence that this alteration takes place before the onset of schizophrenia or elevates the risk for the later onset of schizophrenia.

Neurophysiological Findings

The neurophysiological impact of comorbid cannabis abuse in patients with schizophrenia is largely unknown. However, there is evidence that an alteration of GABAergic and glutamatergic neurotransmission in cannabis abusing subjects is involved. In the following section the results of studies using event-related potentials (ERP), mismatch negativity (MMN) and transcranial magnetic stimulation (TMS) are shortly summarized.

Event-Related Potentials (ERP)

A series of replication studies have shown P50 suppression to be reduced in chronic cannabis users, similar to that seen in schizophrenia [78, 79]. Anandamide (AEA) modulates the α-7-nicotinic receptor, which is linked to P50 suppression, suggesting longer-term effects of smoked cannabis on this system [79]. A similar modulation as in the auditory evoked P50 has been demonstrated in auditory and visual evoked P300, reporting a reduction of the event-related potentials in schizophrenia, including its prodrominal states, and after cannabis use [80–83], probably reflecting reduced inhibition in this cortico-subcortical loop.

Mismatch Negativity (MMN)

MMN is an ERP elicited by any discriminable change by a deviant stimulus within a regular background of repetitive auditory stimuli while attention is directed elsewhere. MMN amplitude is reduced in schizophrenia patients [84]. MMN reduction is thought to be an index of deficient NMDA receptor functioning [84], and anandamide has been shown to modulate NMDA receptor activity directly through proexcitatory potentiating effects as well as indirectly inhibiting activity through cannabinoid receptor–mediated inhibition of voltage-sensitive calcium channels [79]. In one recent study chronic cannabis use leads to reduced MMN amplitude similar to schizophrenia, in particular, duration and quantity of cannabis use could be identified as important factors of deficient MMN generation [85]. Until now, no studies of schizophrenia patients with and without comorbid cannabis abuse are available.

Transcranial Magnetic Stimulation (TMS)

Some neurophysiological studies used paired-pulse transcranial magnetic stimulation [86] to assess mechanisms of intracortical inhibition (SICI) and intracortical facilitation (ICF) in schizophrenia patients. There is strong evidence that SICI is mediated by GABAergic interneurons via $GABA_A$-receptors, and that ICF results from prevailing glutamatergic and weakened GABAergic interneuronal influence [87]. Despite some controversy, a number of TMS studies have linked schizophrenia

to distinct abnormalities of cortical excitability in the motoneural system. This research is mainly pointing towards a GABAergic dysfunction in schizophrenia [88–92]. These results fit to the lower GABA-related transcripts in cortical areas including the primary motor cortex in subjects with schizophrenia [93].

Recently, Wobrock and coworkers showed that schizophrenia patients with a history of cannabis abuse have a reduced $GABA_A$-mediated SICI and an enhanced ICF compared to patients with no cannabis abuse history [30]. In conclusion, there is a link for a pronounced functional alteration of the GABAergic system and glutmatergic system in schizophrenia patients with comorbid cannabis abuse.

In conclusion, there is some evidence that cannabis abuse alters the GABAergic and glutamatergic system similar to patients suffering from schizophrenia, and that this dysfunction maybe even more pronounced in comorbid patients. The mechanisms involved may be complex and are far from being understood, and it is still a question if neurophysiological alterations in comorbid patients result from a dysfunctional endogenous cannabinoid system (eCS) linked to a subgroup of schizophrenia patients or are the consequence of chronic cannabis abuse.

Interestingly, there may be an additional link between deficits in synchronous neural activity in schizophrenia and the involvement of endogenous cannabinoid system (eCS) in hippocampal oscillations, synchronous activity, integration and binding in the gamma range and high-frequency ripple and theta range. Disruption of this synchronous activity could result from either activation of CB1 receptors by exogenous cannabinoids or a dysfunctional eCS [79].

Genetics

Specific genetic factors may moderate the effect of cannabis exposure on the risk for psychosis. Most available studies to date focus on the catechol-O-methyltransferase (COMT) gene, the neuregulin 1 gene (NRG-1) and the canabinoid 1 receptor gene (CNR1) [94].

COMT is an enzyme involved in the breakdown of dopamine in the synapse. A functional polymorphism (Val108/155Met) of the COMT gene results in two allelic variants influencing the efficacy of dopamine metabolism especially in the prefrontal cortex. The valine allele leads to higher expression of COMT and lower levels of dopamine in prefrontal cortex and subsequent increased dopamine levels in midbrain neurons that project to the ventral striatum [95]. In one study carriers of the Val allele were more sensitive to cannabis (delta-9-THC) induced psychotomimetic effects than Met carriers, but this was conditional on prior evidence of psychometric psychosis liability [96]. In an other longitudinal birth cohort study carrying the COMT valine allele leads to a five times higher risk to suffer from psychotic symptoms and twofold increased risk for schizophrenia in adults if cannabis was used frequently in adolescence [78]. Carrying two copies of the methionine allele does not enhance the risk to exhibit psychotic symptoms or schizophrenia if cannabis was used earlier in life [78]. However, these findings could not be replicated in all studies [97, 98].

NRG-1 is involved in neuronal migration, glial differentiation and the expression and activation of neurotransmitter receptors, including NMDA and GABA, and polymorphisms of the NRG-1 gene are discussed to be associated with the risk for schizophrenia [94, 99]. In animal studies, heterozygous NRG-1 transmembrane-domain knockout mice revealed an increased sensitivity to the behavioural effects of cannabinoids compared to the wild type, especially under conditions of stress [99]. Polymorphisms of the NRG-1 gene may also increase the vulnerability of psychosis if cannabis was used early in life, although no human studies assessing this special topic are available to date.

The CNR1 is thought to modulate the striatal response to rewarding stimuli and polymorphisms of this gene seem to be associated with alcohol and intravenous drug abuse [94]. A variety of CNR1 polymorphisms have been studied for associations with schizophrenia, but the results were not conclusive. In one first study there was no effect of CNR1 polymorphism on schizophrenia between those patients who did use and those who reported the use of cannabis at least 1 prior to illness onset [98].

In summary the most interesting genetic interaction effect on cannabis abuse and psychosis belongs to the COMT polymorphism, while other effects of genes potentially interacting with cannabis consumption like the functional polymorphism of the brain-derived neurotrophic factor (BDNF) gene are not assessed in studies until now.

The Role of the Endogenous Cannabinoid System

The endogenous cannabinoid system (eCS) has several important functions that are relevant to schizophrenia. Cannabinoid receptors (CB1) are the most abundant metabotropic receptors in the brain and are involved in many important physiological and behavioural events. They occur in high density at presynaptic terminals in regions involved in cognition, particularly learning and memory, in the hippocampus, prefrontal cortex (PFC), anterior cingulate, basal ganglia and cerebellum [100]. The eCS, via its endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), mediates the flow of information in the brain through retrograde signalling, modulating inhibitory and excitatory neurotransmitter release crucial for synaptic plasticity, depolarization-induced suppression of inhibition or excitation, long-term potentiation (and hence learning), memory and other higher cognitive functions. The system interacts via the cannabinoid 1 (CB1) receptor with various other neurotransmitter systems, including the glutamatergic and dopaminergic system hat have been implicated in the aetiology of schizophrenia. In contrast to other neurotransmitters, the release of endogenous cannabinoids requires the enzymatic cleavage of phospholipid precursors present in the membranes of neurons and other cells. Once released, endogenous cannabinoids activate cannabinoid receptors on nearby cells and are rapidly inactivated by active reuptake and subsequent enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) [101]. At the presynaptic nerve terminal, activation of CB1 receptors by endogenous cannabinoids such as AEA and 2-AG leads to a decrease in membrane permeability

to calcium and potassium ions, as well as to a decrease in the activity of adenylate-cyclase, thereby inhibiting the release of glutamate, dopamine, acetylcholine and noradrenaline (norepinephrine). GABA reuptake is also inhibited. The eCS serves as a retrograde messenger system tuning and regulating the potential hyper- and hypoactivation of the already mentioned neurotransmitter systems.

The way how the eCS may be involved in schizophrenia pathophysiology was elucidated in studies assessing endocannabinoid levels (e.g. AEA) in cerebrospinal fluid (CSF). In the first study, significantly elevated levels of AEA were observed in CSF of schizophrenia patients, suggesting up- or dysregulation of the eCS in acute schizophrenia [102]. This finding was replicated in a larger sample of schizophrenia and otherwise affected psychiatric patients, revealing a significant elevation of AEA in the CSF, but not in serum, of first-episode antipsychotic-naïve patients. It was also demonstrated that AEA levels in CSF were significantly and inversely correlated to psychotic symptoms and to negative symptoms in particular [103]. In addition, patients at risk of psychosis (initial prodromal states of psychosis) showed significantly elevated levels of AEA in CSF already at this stage of the illness and those patients with higher levels of AEA in CSF were less likely to develop schizophrenia during an observational period of 42 months [104]. Interestingly, first-episode antipsychotic-naïve patients with a frequency of cannabis use of more than 20 times in life showed significantly lower levels of AEA in CSF than acute schizophrenia patients with a frequency of cannabis use in life of less than five times [105]. Again, there was a strong significant inverse correlation between AEA in CSF and psychotic-negative symptoms.

These results suggest that chronic and more frequent administration of cannabis (delta-9-THC) in schizophrenia patients may disrupt AEA release and may thereby weaken the proposed inhibitory feedback loop on dopamine-mediated processes.

Besides these discussed effects the eCS is involved in brain development, in the regulation of immune and inflammatory processes, and has some neuroprotective properties against hypoxia and glucose deprivation [106]. How these mechanisms are involved in schizophrenia pathophysiology is still not clear.

Treatment Issues

Assessment of Substance Abuse

Screening and assessment of comorbid substance abuse should be performed systematically in schizophrenia patients keeping the high prevalence of this comorbidity in mind. Assessment should address lifetime history of the use of all substances, amounts, patterns, and circumstances of use, perceived effects of substances, and current stage of motivation and should include a drug screening in urine especially in young male patients [107].

Standardized instruments to assess substance use specifically developed for people with severe mental illness may assist the clinical interviewing [107].

Integrated Treatment

Integrated treatment describes a flexible combination of treatments from the mental health and addiction fields that are blended together in the treatment of an individual with co-occurring mental illness and addiction [108]. An individualized pharmacotherapy is an essential part of an integrated treatment approach combining strategies for improvement of schizophrenia and addiction or abuse in dual diagnosis patients [109]. Ongoing care offered by one experienced team provides the background for treatment success in this special population [108, 110, 111]. The integrated approach should be matched individually to the patient's current state of health, degree of motivation, cognitive and psychosocial resources, and needs and should consider patients' biography and current circumstances [1, 112–114]. As part of integrated treatment besides pharmacotherapy, psychosocial interventions, substance abuse counselling and community supports are needed in an individualized comprehensive package. The brain reward circuitry dysfunction in comorbid patients may be the target for pharmacological and psychosocial treatments aimed at the reduction of substance use in schizophrenia [115].

The key issue in providing treatment for this population is developing a dual disorder approach that integrates treatment of substance abuse and schizophrenia. Many programmes are now providing this integration through interdisciplinary teams with expertise in the treatment of schizophrenia and substance abuse. This form of treatment features assertive outreach, case management, family interventions, housing, rehabilitation and pharmacotherapy. It also includes a stagewise motivational approach for patients who do not recognize the need for treatment of substance use disorders and behavioural interventions for those who are trying to attain or maintain abstinence.

Pharmacological Treatment

In the following section we first summarize the available studies in patients with schizophrenia and comorbid substance abuse and critically discuss the evidence derived from these studies. Afterwards we suggest some pharmacological treatment strategies keeping this evidence in mind.

Of note, the preferred pharmacological strategy depends on the target symptoms: improvement of schizophrenic psychopathology, reduction of craving and substance use, treatment of concomitant symptoms like depressive mood or management of side effects.

Reviewing the Evidence

Treatment with Antipsychotics

Antipsychotics were prescribed for the treatment of schizophrenia over approximately 50 years. In terms of their chemical structure, the antipsychotic medications, frequently known as neuroleptic agents, are a heterogeneous group

of psychoactive drugs (such as phenothiazines, thioxanthenes, butyrophenones, diphenylbutylpiperidines, benzamides, benzisoxazoles and dibenzepines) [14]. "Conventional" or first-generation antipsychotics (FGA) can be classified into high- and low-potency medications. The effective dose of a FGA is closely related to its affinity for dopamine receptors (particularly D2) and its tendency to cause extrapyramidal side effects [116]. High-potency antipsychotics have a greater affinity for D2 receptors than low-potency medications and the effective dose required to treat psychotic symptoms like delusions and hallucinations is much lower than for low-potency antipsychotics. With the detection of clozapine as an effective antipsychotic agent not inducing catalepsy, a new class of "atypical" antipsychotics became established. Because various antipsychotics can be found on a continuum ranging from typical to atypical the terminus second-generation antipsychotics (SGA) for describing these new agents inducing considerably fewer extrapyramidal symptoms (EPS) in a therapeutic dose range than conventional neuroleptics has been found to be more suitable [117].

The advantages of SGAs in treating negative symptoms, cognitive disturbances, and depressive symptoms, seen in the first efficacy studies [118] have recently been doubted in two large effectiveness studies [119, 120]. However, some SGAs induce pronounced metabolic side effects and more weight gain compared to most conventional antipsychotics [14].

The introduction of the second generation antipsychotics (SGAs), with their lower rate of extrapyramidal-motor side effects and assumed subsequently higher treatment adherence rate, was combined with the hope that a more favourable treatment course can also be achieved in the group of schizophrenia patients with comorbid substance use disorder. However, the assumed higher treatment adherence with SGAs compared to FGAs could not be confirmed in effectiveness studies like the CATIE study [119]. Besides determining their antipsychotic effects, the different receptor profiles of the SGAs may possibly contribute to a reduction of craving and thus of drug use [121, 122]. Accordingly, the recently published international guidelines of a task force on biological treatment of schizophrenia recommended preferential use of SGAs to treat this patient group [14]. In the following section the efficacy of antipsychotic agents are described with regard to the available studies and evidence. An overview of the available studies provides Table 15.1.

Orally Administered Antipsychotics

Despite a broad individual clinical experience with the application of oral *FGAs*, there is no controlled study in dual diagnosis patients available comparing one antipsychotic medication with an other. One study demonstrated that patients with the dual diagnosis showed a generally poorer response to treatment with haloperidol and perphenazine [123].

For the comparison of *SGAs* as a group with conventional antipsychotics (FGAs) there are some studies available, most of them using a switch (change from FGAs to SGAs, and comparison versus baseline) or cross-sectional design. In these studies advantages for the reduction of substance abuse were reported, e.g. in a

Table 15.1 Orally administered antipsychotics

Design/Evidence	SUD	No. of patients	Duration	Results/References
Haloperidol/Perphenazine				
1 Prospective open study	"Drugs"	35 pts., SZ/SZP/SA, 13 with SUD	Not specified	• Pts. with additional SUD showed poorer response to treatment [123].
SGAs as group				
1 Prospective open study	Alcohol, "drugs"	362 pts., SZ, 87 pts. with AUD/SUD	6 months	• Pts., compliant with medication, treated with SGAs were less likely to use substances than those receiving FGAs [127].
3 Cross-sectional or retrospective open studies	Alcohol, cocaine, "drugs"	374 pts., SZ-SP-dis. with AUD/SUD	1 month – 2 years	• Less alcohol consumption with SGAs than with FGAs, no difference in psychopathology or EPS [124] • Pts. with long-term SGAs (161) or switched to SGAs (33) showed improvement in alcohol and drug use (4 of 7 ASI-Scores) or in psychological variables [126] • Pts. with risperidone (16) or ziprasidone (14) stayed longer in treatment, and a higher percentage of them completed successfully a dual-diagnosis treatment programme, than those with olanzapine (15) or depot FGAs (10). [125]
Amisulpride				
1 Case report	Alcohol	1 pt., TRS with AUD	25 months	• After adding amisulpride to clozapine, improvement of psychopathology and aggression, "disappearance of addictive behavior" [160]
Aripiprazole				
1 Prospective, open study	Cocaine, alcohol	10 pts., SZ with AUD/SUD	8 weeks	• Significant improvement of psychopathology, less cocaine use than before (9.4 vs. 51.7%), less craving for cocaine and alcohol [158]
1 Case report	THC	1 pt., SZ with SUD	12 months	• 3 months after switching from olanzapine/escitalopram to aripiprazole, cessation of THC use, no relapse [159]

Table 15.1 (continued)

Design/Evidence	SUD	No. of patients	Duration	Results/References
Clozapine				
3 Prospective follow-up studies (one with retrospective analysis of subgroups)	Alcohol, cocaine, THC	291 pts., SZ/SA, 157 pts. with AUD/SUD	6–60 months	• Significantly less substance abuse relapse, but no significantly better symptom improvement with clozapine than with other SGAs/FGAs [128] • Reduction of drug use and increase of motivation level correlated with improvement of psychopathology after switching to clozapine [131] • No difference in the relapse rate between SUD and non-SUD pts. [132]
3 Retrospective open studies	Alcohol, cocaine, THC, polyvalent	413 pts., SZ, TRS, SA, > 81 pts. with SUD	6–36 months	• Comparable reduction of psychopathology in SUD and non-SUD pts., reduction of substance use and craving [129, 130] • Reduced substance use correlated with reduction of symptoms [135] • Less substance use with clozapine (clozapine 0% vs. FGAs 13%) [133]
1 Case series	Alcohol	13 pts., SZ	Not specified	• Substance use reduced in 11 pts. [134]
4 Case reports	Alcohol, cocaine THC, halluc., polyvalent,	5 pts., SZ/SA	4 weeks–5 years	• Reduction of psychopathology and substance use after switching from FGAs [153] • Urine test negative [222] • No relapse of alcohol or drug use [223] • Abstinence after switching [224]
Olanzapine				
4 RCTs	Cocaine, THC, alcohol	83 pts., SZ with SUD, 30 pts. with THC psychoses	1–6 months	• Trend for greater reduction of cocaine-positive urines and significantly fewer self-reported days of use (any drugs) with olanzapine compared to risperidone [139] • Comparable reduction of psychopathology, but more EPS with haloperidol than with olanzapine in THC psychoses [136] • Significant reduction in cocaine use compared to the amount at baseline with olanzapine, and increase with haloperidol. Increase of craving with olanzapine, no difference in psychopathology [137] • Significantly greater reduction of craving (only Energy Score) and greater improvement in PANSS subscale gen. psychopathology with olanzapine than with haloperidol [138]

Table 15.1 (continued)

Design/Evidence	SUD	No. of patients	Duration	Results/References
4 Prospective open studies	Heroin, alcohol, cocaine, THC, halluc., amphet.	152 pts., SZ/SA with AUD/SUD, 61 pts. with SZ/SA on methadone and buprenorphine	3–6 months	• Significantly longer time in treatment, more decrease in SCL-90 score and more negative urine analyses in the olanzapine than in the haloperidol group [143] • 21 of 30 pts. with full remission of substance abuse, 9 partial; improvement of psychopathology [140] • Reduction of severity of substance abuse and psychopathology [141] • Less substance abuse after switching to olanzapine [142]
1 Prospective RCT with retrospective analysis of subgroups	THC, alcohol, cocaine, halluc. opiates	262 pts., FE-SZ, 37 with SUD (lifetime)	3 months	• Pts. with comorbid alcohol use showed poorer response to olanzapine, however, higher drop-out rate among SUD pts. receiving haloperidol [145]
Retrospective open study	Alcohol, THC, PCP, cocaine, polyvalent	60 pts., TRS, 23 with SUD (lifetime)	7 weeks	• No difference between pts. with and without SUD [146]
Prospective open study	Cocaine	4 pts., SZ with SUD	–	• Greater reduction of psychopathology and craving with olanzapine than with haloperidol [155]
Quetiapine				
1 Prospective RCT, switch study	Cocaine, amphet.	24 pts., 9 with SZ/SA	3 months	• After switching from FGAs to quetiapine: reduced craving, no improvement of psychopathology, no difference in amount of use [225]
1 Prospective, open, switch study	THC, alcohol, others	24 pts., SZ-SP-dis.	3 months	• Reduced substance use for SUD (no. of days, severity, urine screening for SUD) and craving, significant improvement of cognition, psychopathology and depressive symptoms after switching to quetiapine [148]
1 Case series	THC	8 pts., 4 SZ, 4 bipolar	6 months	• Reduced substance use [149]
1 Case report	Alcohol, cocaine	1 pt. , SZ	> 5 months	• Reduction of psychopathology and improvement of social functioning, abstinence [150]

Table 15.1 (continued)

Design/Evidence	SUD	No. of patients	Duration	Results/References
Risperidone				
1 Prospective RCT	THC	30 pts., THC-induced psychotic disorder	1 month	• No difference in the reduction of psychopathology (BPRS), no difference in EPS between risperidone and haloperidol [151]
2 Prospective open studies	Cocaine, alcohol	79 pts., 18 SZ with SUD (cocaine), 61 SZ with AUD	6 weeks–24 months	• Greater reduction of psychopathology (trend: PANSS negative subscale., PANSS total subscale), of substance use and craving with risperidone compared to FGAs, 6 weeks [152] • In 2 years, significantly more pts. receiving risperidone readmitted to hospital than those receiving clozapine (75 vs. 48%) [157]
1 Retrospective open study	Alcohol, THC	41 pts., SZ/SA with SUD/AUD	12 months	• Significantly more pts. stopped substance use with clozapine (54%) than with risperidone [156]
1 Case series	Alcohol, cocaine, opiates, polyvalent	14 pts., SZ/SA with SUD	Up to 9 weeks	• No clinical improvement in 11 of 14 pts., risperidone overall well tolerated [226]
2 Case reports	Cocaine, codeine, ephedrine	3 pts., SZ with SUD	2–10 months	• After switching from FGAs to risperidone, reduction of craving and cocaine use, psychopathology unchanged [155] • Reduction of psychopathology, substance use and craving [154]

Abbreviations: Pts. = patients; SZ = schizophrenia; SZP = schizophreniform disorder; SA = schizoaffective disorder; SZ-SP-dis. = Schizophrenia spectrum disorder: SUD = Substance Use Disorder; AUD = Alcohol Use Disorder; FGAs = First Generation Antipsychotics; SGAs = Second Generation Antipsychotics; RCT = Randomized Controlled Trial; PANSS = Positive and Negative Syndrome Scale; EPS = extrapyramidal motor symptoms; BPRS = Brief Psychiatric Rating Scale; THC = Tetrahydrocannabinol; Amphet. = Amphetamines; Halluc. = Hallucinogens; ASI = Addiction Severity Index

cross-sectional study showing comparable reduction of psychopathology as well as less alcohol use in the group of patients being treated with SGAs than those receiving FGAs [124]. In another retrospective study analysing the medication data of patients participating in an inpatient dual diagnosis treatment program, patients taking risperidone (mean 3.9 mg/d) or ziprasidone (mean 132.8 mg/d) stayed longer in the treatment program and completed it successfully to a higher percentage than patients with olanzapine (mean 18.7 mg/d) or fluphenazine and haloperidol decanoate [125]. However, a retrospective chart review showed after adjusting for confounding factors no significant difference in the reduction of alcohol and drug use after switching from FGAs to SGAs compared to continued treatment with FGAs [126]. In one recent naturalistic prospective study treatment with FGAs (clozapine, olanzapine, risperidone) resulted in significantly reduced probability of substance use in the 6-months follow-up period [127].

Looking at the studies comparing individual antipsychotics, there is a large number of studies available for the SGA *clozapine* demonstrating a reduction of substance abuse after switching from FGAs or during clozapine treatment, compared with treatment with FGAs [128–134]. Unfortunately this experience is limited to open prospective studies or retrospective analysis, no randomised controlled study could be identified. In most of these studies, the reduction of substance abuse during treatment with clozapine was associated with the improvement of clinical symptoms [131, 135]. In one retrospective analysis of data, treatment with clozapine prevented psychotic relapse to the same degree in patients with treatment-resistant schizophrenia and concomitant drug abuse as in the group without substance use [132].

For *olanzapine*, there are 4 randomised controlled studies available, 3 comparing olanzapine to haloperidol treatment [136–138] and one study in comparison to risperidone [139]. In the first randomised, double-blind study olanzapine was as effective as haloperidol, but caused fewer extrapyramidal symptoms (EPS) in patients with cannabis-induced psychosis [136]. In one more recent, double-blind RCT similar results were observed in dual diagnosis patients. In the olanzapine group there was no superior improvement of psychopathology, but a lower rate of extrapyramidal symptoms and a superior reduction of cocaine abuse, but increased craving compared to haloperidol [137]. In another double-blind RCT in cocaine-dependent schizophrenia patients, significant superior psychopathological improvement with olanzapine compared to haloperidol in the "general psychopathology" subscale of the PANSS and a significant reduction of craving, at least in one subscale (energy), was reported [138]. In the double-blind, randomised study comparing olanzapine with risperidone, the olanzapine group showed a trend for a greater reduction of the cocaine-positive urines [139].

In prospective open studies psychopathology as additional substance use improved in patients with schizoaffective or schizophrenic psychosis after switching from FGAs to olanzapine [140–142]. In another open study heroin-dependent patients with comorbid schizophrenia revealed more negative urine analyses for illicit drugs with olanzapine than with haloperidol and remained longer in treatment [143]. Case series demonstrated superior improvement of psychopathology

and craving [144] and a retrospective analysis of a prospective first-episode study reported a lower drop-out rate [145] with olanzapine compared with haloperidol. In addition, olanzapine was shown to be as effective in patients with treatment-resistant schizophrenia and concomitant drug use as in patients without comorbid substance abuse [146].

In a randomised, controlled study no significant advantage in psychopathology and the frequency and amount of drug use, but in the extent of craving, was found in patients switched to *quetiapine* compared with those remaining on FGAs [147]. However, an open, prospective switch study showed a reduction of cannabis use and craving, accompanied by an improvement of psychopathology, depressive symptoms and cognition [148], similar to a case series and a case report showing an improvement of psychopathology with quetiapine and evidence for a reduction of substance use [149, 150].

In a randomised, controlled study *risperidone* was not superior to haloperidol in patients with a cannabis-induced psychotic disorder [151]. In contrast, an open, prospective study with risperidone compared with FGAs demonstrated a trend towards improvement of psychopathology and a reduction of both drug use and craving in the risperidone group [152]. Case reports and case series reported an improvement of psychotic symptoms after switching to risperidone [153, 154], although this was not the case in two patients [155]. The retrospective head-to-head comparison of risperidone and clozapine showed a higher rate of abstinence with clozapine in schizophrenia patients with alcohol and cannabis abuse [156]. In addition, a prospective naturalistic study demonstrated a significant lower remission rate with clozapine than with risperidone in schizophrenia patients with comorbid alcohol use disorder [157]. The reason for hospitalisation and the amount of alcohol consumption in the 2-year follow-up period was not described in this study.

In the only prospective open study with regard to *aripiprazole*, significant improvement of psychopathology, less cocaine use, less craving for cocaine and alcohol, and improvement of psychotic symptoms could be seen after switching to aripiprazole [158]. In one schizophrenia patient cannabis use diminished after switching from olanzapine to aripiprazole and escitalopram treatment could be stopped [159].

There is only one case report available using *amisulpride* as an add-on treatment to clozapine in a treatment-resistant schizophrenia patient with comorbid alcohol dependence, resulting in “disappearance of addictive behavior” and improvement of psychopathology [160].

Interestingly, the subgroup analyses of the CATIE study revealed no advantage for the group of patients using illicit drugs and randomised to olanzapine compared to perphenazine, risperidone, quetiapine and ziprasidone, in terms of treatment discontinuation [161]. In contrast, this advantage for olanzapine patients found in the whole study sample, was also evident in the subgroup of schizophrenia patients avoiding illicit substances. After adjustment for differential treatment duration there was no difference in symptom reduction or global improvement between substance users and non-users.

Depot Antipsychotics

There are some open, not randomised studies available concerning the efficacy of FGAs in depot formulation (see Table 15.2). Patients with additional alcohol use disorder demonstrated significantly more positive and fewer negative symptoms, a tendency to higher doses but lower plasma levels and received in a significantly higher percentage anticholinergics during treatment with fluphenazine decanoate than those without comorbidity [162]. Improvement in psychopathology when switched to flupentixole decanoate in patients with schizophrenia and comorbid cocaine or alcohol use was reported in a few case reports and prospective follow-up studies without a control group [163–166]. A slight reduction of substance use and craving was also observed in these studies (see Table 15.2).

For SGAs, until now, there is one open, randomised, controlled study of long-acting risperidone (risperidone microspheres) versus a depot preparation of a FGA (zuclopentixole decanoate) available [167]. In this rater-blinded study significantly less drug use (urine tests), as well as a longer time until relapse to drug use, and better compliance in the Substance Abuse Management Program was shown with risperidone. This was accompanied by a superior improvement of psychopathology (PANSS negative subscale and general psychopathology subscale) and less EPS compared to the zuclopentixole group.

Antidepressive Agents

Treatment with antidepressants added as an adjunct to antipsychotics in schizophrenia is indicated when depressive symptoms occur meeting the syndromal criteria for major depressive disorder or causing severe and significant distress (e.g., when accompanied by suicidal ideation) or interfering with function [168]. Another indication is the persistence of negative symptoms not responding to the switching of antipsychotics [168]. One reason for the use of antidepressants in schizophrenia patients with comorbid substance use is that depressive mood may lead to the use of addictive substances as a result of attempted self-medication [169]. On the other hand sedative antidepressive agents were used to treat withdrawal symptoms and craving in substance dependence. This builds the background for conducting studies with antidepressive add-on treatment. There were three randomised, controlled studies available investigating the efficacy of antidepressive pharmacotherapy in schizophrenia patients with comorbid cocaine abuse [170, 171]. The tricyclic agent desipramine, administered adjunctive to antipsychotic therapy, leads to reduced craving [172] and cocaine use [171]. In dysphoric schizophrenic patients the administration of imipramine was effective in reducing the use of cocaine but not of cannabis, while depressive symptoms did not improve [170].

Mood Stabilizers

In schizophrenia there are a few indications for augmenting antipsychotic pharmacotherapy with mood stabilisers. There is limited evidence that augmentation

Table 15.2 Antipsychotics with depot formulation

Design/Evidence	SUD	No. of patients	Duration	Results/References
Fluphenazinedecanoate				
1 Retrospective open study	Alcohol	38 pts., SZ, 19 with AUD	Not specified	• Significantly more positive and fewer negative symptoms, and more use of anticholinergics in pts. with AUD [162]
Flupenthixoldecanoate				
2 Prospective open studies	Alcohol, cocaine	27 pts., SZ with AUD; 8 pts., SZ with SUD (cocaine)	10 weeks–6 months	• Significant reduction of alcohol use and craving, slight improvement in the PANSS, but 50% marked or very marked improvement in CGI compared to baseline [166] • Improvement of psychopathology (PANSS, BDI); no. of urine samples positive for cocaine and consumption reduced compared to baseline (in 5 of 8 pts.) [163]
1 Prospective case series	Alcohol, THC, benzod., amphet.	20 pts., SZ/SA, 7 with SUD	12 months	• 6 of the 7 pts. remained abstinent during the period of observation; improvement of psychopathology compared to baseline [164]
1 Case report	Alcohol	1 pt., SZ with AUD	12 months	• Remission of psychopathology, alcohol abstinence, reduction of craving [165]
Risperidone microspheres				
1 Prospective open RCT (rater-blinded)	SUD	115 pts., SZ with SUD	24 weeks	• Significantly less drug use (fewer positive urine samples) with risperidone microspheres, greater improvement of psychopathology (PANSS), EPS and compliance in Substance Abuse Management Program than with zuclopenthixol decanoate [167]

Abbreviations: Pts. = patients; No. = number; SZ = schizophrenia; SA = schizoaffective disorder; SUD = Substance Use Disorder; AUD = Alcohol Use Disorder; RCT = Randomized Controlled Trial; PANSS = Positive and Negative Syndrome Scale; EPS = exptrapyramidal motor symptoms; BDI = Beck Depression Inventory; THC = Tetrahydrocannabinol; Amphet. = Amphetamines; Benzod. = Benzodiazepines; CGI = Clinical Global Impressions

with mood stabilisers or anticonvulsants reveals benefits for patients with treatment resistance, after other therapy options have been exhausted [168]. In special circumstances adding mood stabilisers may be useful, e.g. valproate may be a therapy option if aggression and hostility is predominantly present and lithium may reveal benefits if depressive symptoms are predominant. If treatment is not sufficient to treat the symptoms of excitation/tension or anxiety, additional treatment with carbamazepine, valproate or lithium may be considered [14]. There is some evidence that lamotrigine as an adjunctive treatment, especially to clozapine, can reduce schizophrenic psychopathology. The add-on treatment with lamotrigine was associated with a significant reduction of alcohol consumption and craving in a first case series including treatment-resistant schizophrenia patients with comorbid alcohol use disorder [173]. In alcohol addiction carbamazepine is used to treat alcohol withdrawal symptoms and to prevent withdrawal seizures [15].

Anti-craving Agents

Anti-craving agents and drug antagonists have been used in the treatment of positive symptoms of schizophrenia. This strategy based on the hypothesis that the endogenous opioid system may be involved in the pathophysiology of schizophrenia [174]. Initial positive results in previous investigations, i.e. an improvement of negative or positive symptoms with opiate antagonists such as naloxone, naltrexone and nalmefene, could not be confirmed in subsequent studies. In these studies sometimes a worsening of schizophrenia symptoms could be observed (e.g. [175]).

In schizophrenia patients with comorbid alcohol abuse disorder a significant reduction of drinking days and less craving during treatment with naltrexone, a long-acting opioid receptor antagonist, could be demonstrated in a randomised, double-blind, placebo-controlled study [176]. There was no worsening of psychotic symptoms with naltrexone. In a retrospectively analysed open study augmentation of antipsychotic treatment with naltrexone led to a reduction of alcohol consumption in schizophrenia patients with comorbid alcohol abuse or dependence [177]. In a prospective open study a significant decrease of alcohol use and alcohol craving in combination with an improvement of psychopathology could be observed when administering naltrexone on three days a week, but alcohol related biomarkers did not improve [178].

Disulfiram

In contrast to anti-craving agents disulfiram works by inhibiting alcohol dehydrogenase, which results in an accumulation of acetaldehyde and activation of an intolerability reaction in the case of alcohol consumption. Disulfiram is used for relapse prevention in alcohol-dependent patients since several decades.

In schizophrenia patients with comorbid alcoholism patients receiving disulfiram remained longer in a special treatment programme and spent fewer days in hospital [179]. This first follow-up study found no relevant complications in these patients

and a compliance similar to that in alcohol-dependent patients without underlying schizophrenia. A retrospective analysis of two centres that offered integrated programmes for dual diagnosis patients showed an increased abstinence rate for alcohol use and fewer inpatient treatment days after starting treatment with disulfiram [180]. However, disulfiram may itself induce psychoses, probably due to its blockade of dopamine-beta hydroxylase [181, 182]. For this reason, the use of disulfiram in patients with schizophrenia and comorbid alcohol dependence is a matter of controversy, although the studies performed in dual diagnosis patients have so far not found a clinically relevant worsening of the psychotic symptoms. It should also be considered that disulfiram can accelerate the metabolism of antipsychotics.

Treatment Recommendations

Treatment with Antipsychotics

The application of antipsychotics is a mainstay of treatment for schizophrenia patients with comorbid substance abuse. There is no need to use higher doses of antipsychotics than in patients without this comorbidity. Higher doses do not necessarily result in a complete disappearance of psychotomimetic effects of drugs, even if they have successfully treated schizophrenic symptoms in the patient's history [21, 183]. Psychostimulants may provoke symptoms when antipsychotic therapy is actually adequate [184, 185].

If SGAs are superior to FGAs in this special patient population is a matter of debate. Recent reviews increasingly recommend SGAs as a superior treatment alternative to FGAs [186–188], and describe the advantages of these newer compounds for patients with comorbid substance use disorder by means of the different receptor profiles [189]. Indeed, the available studies suggest that oral SGAs (aripiprazole, clozapine, olanzapine, quetiapine, risperidone) may be superior to FGAs in treating certain psychopathological symptoms, and in reducing craving and drug consumption, nevertheless the evidence for this is weak. The most studies describing positive effects in reducing substance use were conducted with clozapine, although these studies were mostly performed retrospectively. The decrease in drug consumption was often accompanied by improvement of psychopathology. Patients with improved symptoms may tend to use drugs less frequently, and this may be independent of a hypothesized effect on brain reward circuitry. However, non-compliance, which is often a major problem in dual diagnosis patients, may be an argument against the preferential administration of clozapine. If clozapine intake is interrupted for more than 3 days, it has to be uptitrated similar to the initiation of that drug regime due to the otherwise increased risk of neutropenia.

While patients with a dual diagnosis have a lower rate of adherence to pharmacotherapy [190], in most reviews the use of depot formulations (haloperidol or flupentixole decanoate) is considered to be a favourable therapy option (e.g. [121]). No prospective controlled long-term studies have been performed on relapse prevention of schizophrenia in patients with a dual diagnosis so far. Prospective,

open studies been performed with risperidone and aripiprazole, demonstrating a slightly superior effect of these SGAs on the reduction of substance use and craving compared to FGAs [152, 158]. The performed randomised controlled studies with olanzapine, quetiapine and risperidone microspheres, showed slight but not really remarkable advantages for these SGAs compared with FGAs [137, 147, 148, 167]. These findings may support the hypothesis of a neurobiologically determined dysfunction of the dopaminergic reward system in both, schizophrenic patients and people with substance addiction [191]. A highly potent blockade of dopamine D2 receptors (e.g. with conventional antipsychotics), could result in a further intensification of this dysbalance and thus in an increased use of the addictive substance [186]. The broader receptor profile of the SGAs, with their additional effects on the serotonergic system and reduced dopamine blockade in the mesocortical area, contributes to their better efficacy in treating negative and depressive symptoms in several (but not all) studies and the assumed lower rate of pharmacogenic dysphoria. Due to this more theoretical assumption and slight advantages for the improvement of psychopathology and decrease of substance use in some studies, the preferential use of SGAs in this comorbid patient group is recommended, although the evidence is weak.

Augmentation Strategies to Reduce Substance Use and Craving

This hypothesis of dysphoria leading to increased drug intake is supported by the finding that in schizophrenia patients with comorbid substance use antidepressive pharmacotherapy with TCAs such as imipramine or desipramine, resulted in reduction of substance use [170] accompanied by an improvement of depressive symptoms, at least in patients with a postpsychotic depression [172]. Until now, there are no studies with newer antidepressive compounds, e.g. selective serotonin reuptake inhibitors (SSRIs), available confirming these results. However, it is quite possible that such substances would have positive effects, although there is no convincing evidence for SSRIs to reduce drug consumption in non-depressive patients with substance related disorders [15]. In conclusion, antidepressants (proven efficacy for TCAs such as desipramine and imipramine) can be given adjunctive to neuroleptic maintenance treatment as a therapeutic attempt to reduce craving in schizophrenic patients with comorbid substance use, especially cocaine misuse. There is an urgent need studies evaluating the efficacy of SSRIs or SNRIs this patient group.

Anti-craving substances (naltrexone) and disulfiram seem to have a positive influence on substance use in schizophrenic patients, similar to that in addicted patients without schizophrenia (e.g. [178, 192]). However, it is important to remember that disulfiram itself can induce psychoses, probably due to its blockade of dopamine-beta hydroxylase [181, 182]. For this reason, the use of disulfiram in patients with schizophrenia and comorbid alcohol dependence is a matter of controversy, although the studies performed in dual diagnosis patients have so far not found a clinically relevant worsening of the psychotic symptoms. It should also be considered

that disulfiram can accelerate the metabolism of antipsychotics. These arguments support the preferential use of naltrexone in this specialized population of patients.

Management of Intoxication and Withdrawal

In clinical practice the treatment of intoxication or withdrawal symptoms in patients with a dual diagnosis of schizophrenia and substance use disorder does not differ from treatment of intoxicated patients without schizophrenia (e.g. [1, 121]). However, it should be considered that interactions may occur if the patient is already receiving antipsychotics. Benzodiazepines are useful for alcohol withdrawal symptoms because they show relatively few pharmacological interactions with other psychopharmaceutical agents. Furthermore, they may protect the occurrence of convulsions caused by withdrawal and the development of delirium, while concomitant antipsychotic medication (particularly clozapine and zotepine) can lower the convulsion threshold [121, 122]. Carbamazepine may serve as an alternative treatment for alcohol withdrawal syndrome in schizophrenia, but should not be combined with clozapine due to the increased risk of leucopenia [121, 193].

Minimizing Side Effects

This patient group also may have a higher risk of developing extrapyramidal side effects [194], and a possibly additive effect for orthostatic hypotension. In consequence to this carefully dosing and closely monitoring for EPS and blood pressure is needed. The early in the course administration of anticholinergics in case of EPS may increase the medication compliance with antipsychotics. Certain substances, for example resorbing substances stored in fatty tissue, can cause pharmacokinetic interactions and continuing psychotic symptoms, especially in the first phase of treatment, so that the patient may appear to be resistant to treatment without this actually being the case. Therefore drug screening in urine may be performed still after symptoms of intoxication have disappeared. While alcohol has been found to be responsible for a reduction of the plasma levels of antipsychotics, drug monitoring in these patients is recommended [162]. When clozapine is administered to patients with cocaine use, the treating physician must consider the possible interaction of the two substances and closely monitor the patient for possible circulatory problems while introducing clozapine [195]. In the conducted studies with antidepressants, one patient experienced an exacerbation of psychotic symptoms [170], but this complication seems to be extremely rare and could adequately be treated by adjusting the dose of antipsychotic medication. Physicians should be aware of the possible triggering of hypertensive crises when using antidepressants to treat patients with concomitant use of drugs with adrenergic stimulation [185]. For this reason, monoamino-oxidase (MAO) inhibitors should not be used in this patient group.

Psychological and Psychosocial Interventions

Psychological and psychosocial interventions that are essential for effective treatment in patients with double diagnosis and especially schizophrenia and comorbid substance abuse include engagement strategies, motivational counseling, stage-wise interventions, active treatment, long-term program retention, integrated mental illness and substance abuse treatments, and relapse-prevention strategies. Further comprehensive services, such as peer support, family education and interventions, liaison with the criminal justice system, housing, and vocational rehabilitation, should also be available, along with specialized programs for those with more complex disorders, cognitive impairment, and treatment resistance. Nevertheless, that the evaluation of combined treatment programs with motivational elements, psychoeducation and cognitive-behavioural approaches shows an effect in reducing substance abuse and in decreasing frequency and severity of psychotic decompensations, there seems to be only a slight advantage over the comparison group (often "treatment as usual"). In the following section the key principles of psychosocial and psychological treatment strategies, an overview of the evidence for the usually preferred psychological strategies and a short recommendation is given. The psychological interventions for the dually diagnosed people are typically derived from strategies used in clients with substance use disorders adapted to the specific circumstances in this special population (e.g. cognitive impairment, disturbed communication abilities, reduced drive). The features of psychosis may inhibit progress in any treatment phase. Positive symptoms such as delusions, auditory hallucinations, concrete thinking, or inferential thinking can create barriers, as can negative symptoms such as flat affect, low energy levels, decreased goal-directed activity, and a limited range of emotional expressivity.

Steps to Begin with Treatment

After establishing a substance use disorder diagnosis in patients with schizophrenia spectrum disorders, it is necessary for treatment planning to evaluate the patterns of use for every single substance. The usage of a standardized interview like the time-line follow-back interview [196] seems to be helpful, especially when trying to evaluate a linkage of substance abuse and psychotic symptoms in an individual. Besides the misuse of illegal substances the consumption of nicotine and caffeine, which is quite common is this special population, should be evaluated concerning the additional health problems caused by these legal substances.

The most widely used model for motivation in the population with substance use disorders was developed by Prochaska and DiClemente and includes five stages of readiness to change: precontemplation, contemplation, preparation, action, and maintenance [197]. Related to this model the next step in treating dually diagnosed patients is to assess the motivational stage of the subject and to estimate the motivation to change the substance abuse pattern starting with declining the amount and frequency of the used substances. A primary goal could be to attain or maintain

abstinence for only one or more of the substances used. In most schizophrenia patients the need for treatment regarding the substance use disorder seems to be very limited and therefore the motivation for change seems to be rather low in this population (e.g. [198]). On the other hand these attitudes are not necessarily trait parameters and should be monitored regularly throughout the course of the treatment awakening the awareness for behavioural change. It should be recognized that in substance use disorder as well as in comorbid patients behavioural change is still a longitudinal process.

The patients with diagnosis of a schizophrenia spectrum disorder and comorbid substance use disorder should be involved actively in terms of a "shared-decision making" in the planning of the next treatment steps. The incorporation of family and friends is recommended to maintain long-time adherence to a treatment program and to enhance the therapeutic alliance with the patient.

Motivational Interviewing (MI)

MI widely regarded as an essential tool when beginning to work with a double-diagnosed patient (e.g. [199]) and a major component of any dual disorder treatment program. It emphasizes personal choice, responsibility and the risks and benefits of ongoing substance abuse and respects the readiness to change. The therapist fortifies the patient and refers to the personal strengths of the patient and may be able to shift commonly low motivation of change to the next higher level. This should lead to the development of an individual treatment plan which also may be written down. The inclusion of the patients' personalized feedback and focussing of special needs and cognitive impairment of patients with a diagnosis of schizophrenia spectrum disorder has lead to many improvements regarding the traditional MI [200] and is often labelled as a Modified Motivational Enhancement Therapy (MET) [112, 201, 202]. An adapted MET for patients with schizophrenia spectrum disorders and other serious mental illnesses could include the development of a working alliance, helping the patient evaluate the pros and cons of substance use (decisional balance), formulating individualized goals, encouraging an environment and lifestyle that are supportive of abstinence, and teaching skills for managing crises. A review concluded that the more sessions are spent with motivational approaches, the better the outcome in terms of harm reduction or abstinence rates seems to be [203]. The modified MET approach includes higher levels of therapist activity and uses behavioural strategies that involve briefer, more concrete language, more repetitions, and the need to pay particular attention to the patient's alertness and adapt the interventions according to the level of alertness.

There are only few studies available concerning the efficacy of MI in schizophrenia patients with comorbid cannabis abuse. In a randomised controlled study (RCT) Martino and colleagues [204] showed superiority of TAU vs. MI resulting in fewer days of cannabis abuse in TAU group. In another RCT Edwards et al. [205] compared MI with psychoeducation (PE) and demonstrated a similar efficacy of both interventions. In contrast to these results, most of the not randomised follow-up

studies without control group revealed positive effects of MI regarding reduction of cannabis abuse or craving scores (see [206]). For instance, Addington and Addington [207] showed a significant advantage of MI in combination with case management on cannabis abuse scores.

Cognitive Behavioural Therapy (CBT)

When the patient is motivated for a change in the substance abuse pattern or expresses the wish to attain or maintain abstinence after several sessions of MI or MET, CBT can be used individually or in group sessions for reaching further treatment goals. Cognitive behavioural techniques in this framework include providing information about craving and triggers of substance abuse, improvement of social skills and introduction of problem-solving strategies. The amount of information and duration of single sessions might have to downsized due to cognitive impairment of this special population. In a modified CBT skill-building is often practiced in small group sessions. Groups are highly structured, and early successes are strongly reinforced to enhance self-efficacy. The therapy accommodates the cognitive limitations of schizophrenia by focusing on a small number of specific skills. Abstinence may be reinforced by providing positive reinforcement (i.e., small amounts of money) for drug-free urine test results.

Hjorthhoj and colleagues [206] reviewed the available studies comparing the efficacy of CBT, MI and treatment as usual (TAU) in patients with schizophrenia and comorbid cannabis abuse. They concluded that insufficient evidence exists on treating this form of dual-diagnosis patients. Most of the identified eleven studies showed ineffective efficacy when cannabis consumption was measured as separate outcome but superiority of CBT when abuse of other substances were grouped together with cannabis consumption. Only five of these eleven studies were randomised controlled trials. Baker et al. [208] found only a slight trend (not significant) towards a reduction of numbers of days using cannabis when comparing combined CBT and MI against TAU. Craig et al. [209] found no statistical difference in consumption patterns between these two groups in their study.

Social Skills Training

Shaner et al. [210] demonstrated a significant decline of the mean number of cannabis-using days at follow-up after a combined intervention with psychoeducation (PE), case management (CM) and skills training (ST). The Substance Abuse Management Module (SAMM) [211] used in that trial is based on relapse prevention, harm reduction, and social skills training. It incorporates a limited subset of skills (e.g., dealing with craving) that are believed to be crucial to drug avoidance and disease management, and it relies on repeated skills practice. This program based on the principles of social skills training and includes a focus on enhancing

problem solving and communication skills to promote healthier recovery and abstinence from substances. One important element is the use of role playing in group treatment sessions in which the group consider ways to address the problem and have peers model how to manage the problem. The therapist could coach the group and provide positive feedback and helpful constructive criticism for those involved in the role play.

Psychological Intervention Manuals

Several clinical therapy manuals have been developed for the treatment of schizophrenia and co-occurring addiction. Used programs in the United States and United Kingdom are the Dual Recovery Therapy (DRT) approach [212], modified cognitive-behavioural therapy (CBT) [213], modified motivational enhancement therapy (MET) [112], and the Substance Abuse Management Module (SAMM) [209, 210]. These approaches seem to be more similar than different, since they all include elements of motivation, relapse prevention, and social skills training. For instance, the Dual Recovery Therapy (DRT) integrates substance abuse relapse prevention, psychiatric social skills training, MET, and the "recovery language" of 12-step programs in linked group and individual treatment sessions.

In Germany most used manuals combining elements of psychoeducation, motivational interviewing, cognitive behavioural therapy and skills training are the program GOAL, designed for patients with schizophrenia and addiction [214] and a less elaborated therapy manual primarily focussing on psycheducation for patients with the comorbidity of psychosis and addiction [215]. The GOAL program contains four modules during the 5 weeks of treatment. The first module consists of 10 sessions psychoeducation (for details see Table 15.3) including cognitive behavioural elements (CBT) and strategies of motivational interviewing (MI). The second module contains 5 sessions social skills training (SST) including role plays dealing with crucial situations (e.g., meeting substance abusing peers, getting into stressful situations with increased craving). The third module is designed to enhance self efficacy, self consciousness and emotional support by performing art and occupational therapy. During these five sessions patients should express their inner emotions related to their previous life complicated by their substance abuse. The last module consists of 20 sessions physical exercise for general activation, to reduce hidden aggressions, to normalize body experiences and to trust again in own physical and mental abilities. The latter is improved by increasing continuously the physical capacity during the aerobic training.

Other Psychosocial Interventions

There are other psychosocial treatment approaches related to the national health care systems available in this special population. For instance, assertive community

Table 15.3 GOAL program: psychoeducation module

No. of session	Contents of session
1	Introduction of participants and defining of individual treatment goals
2	Explaining effects and consequences of substance use. Trying to find out reasons and individual backgrounds for using substances. Talking about personal experiences of the participants (Motivational Interviewing).
3	Introducing the concept and mechanisms of substance abuse/dependence. Identifying dysfunctional beliefs about consuming substances.
4	Facts about the interface between substance consumption and psychosis.
5	Identifying high risk situations for substance use and craving. Developing skills to manage these situations and getting craving under control.
6	Defining lapse and relapse, learning how to stop substance use and to seek for treatment
7	Strategies of crisis intervention and working out individual plans in case of emergency. Defining a representative or person of trust to assist the patient in case of emergency.
8	Activities to improve mental and physical health, finding hobbies and establishing social relationships instead of using substances. Improving dysphoric and depressive mood without using substances.
9	Weighting advantages and disadvantages of substance use. Encouraging abstinence and rewarding yourself if reaching stopovers. Benefits of living without substance use.
10	Finishing therapy and consolidating previously defined treatment goals. Reminding the skills.

treatment (ACT) in dually diagnosed patients is usually described as a structured health care service approach, in particular by adapting a conventional model of case management to the needs of this client cohort. Studies found effects in people with severe mental illness and co-occuring substance use disorder of assertive community treatment (ACT) [216–218] and of community mental health centres with or without case management (CM) [219], but not differential effects compared with TAU. In a prospective, uncontrolled study ACT was found somewhat effective [220], but the effects were weak.

Conclusions and Future Directions

Systematically assessment of substance abuse should be performed in young schizophrenia patients including urine drug screening. Therapeutic interventions have to be embedded in an individualized integrative approach aiming at the improvement of schizophrenia psychopathology, social functioning and reduction of substance use. Despite the growing prevalence of dual diagnosis patients there are only few controlled studies in this patient group available. Most of the pharmacological studies identified in an extensive literature research were case series, retrospective analyses of medical records or open, prospective case-control studies.

In consequence, the empirical evidence for distinct treatment recommendations in schizophrenia patients with comorbid substance abuse is weak and there is an urgent need for randomised controlled studies in this issue.

Since second generation antipsychotics are at least as effective as first generation antipsychotics in treating positive symptoms, and they appear to be superior in the treatment of negative and cognitive symptoms in schizophrenic patients without comorbid substance use, they might also be favoured for patients with a comorbid substance use disorder. Studies in this patient group suggest that oral SGAs (aripiprazole, clozapine, olanzapine, quetiapine, risperidone) may be superior to FGAs in treating certain psychopathological symptoms, and in reducing craving and drug consumption. As comorbid patients show poorer compliance overall, depot formulations of antipsychotics are of certain interest in this area and should be offered to dual diagnosis patients. There is a hint that SGA depot formulation may be superior to FGA depot formulation in reducing substance abuse, however the evidence for this is limited. Augmentation strategies include the administration of antidepressant to improve dysphoric mood and reduce substance abuse and the administration of anti-caraving substances. A handful of studies suggest that antidepressants given adjunctive to neuroleptic maintenance treatment have some efficacy (e.g. TCAs, such as desipramine and imipramine) to reduce craving in schizophrenic patients with comorbid cocaine use. Studies with both, anti-craving substances (naltrexone) and disulfiram, have also delivered positive results in patients with comorbid alcoholism, but for disulfiram the potential risk of inducing psychosis has to be considered.

In daily practice, after the assessment of the pattern and amount of abused substances, the clinician should offer an oral SGA with favourable side effect profile in the individual patient as first choice. If there is any doubt about the medication adherence the antipsychotic medication should be switched to a SGA depot formulation (or alternatively FGA depot antipsychotic). When symptom improvement is insufficient or treatment resistance is diagnosed clozapine should be introduced if there is no contraindication and regular controls of blood cell counts are ensured. In individual patients it may necessary to combine a depot antipsychotic with an oral SGA, e.g. clozapine. In patients with improved psychopathology but unchanged or increased craving/substance use the augmentation with antidepressants should be considered, especially in patients suffering from postpsychotic depression or dysphoric mood. In the case of alcohol craving or persisting consumption the add-on administration of naltrexone or acamprosate can be recommended, keeping the theoretical worsening of psychotic symptoms with acamprosate as GABA modulating drug in mind.

However, antipsychotic treatment builds the basis for pharmacological augmentation strategies, but pharmacotherapy is only one element in a comprehensive package of interventions including motivational interviewing, cognitive behavioural therapy, community support, housing supports and other psychosocial therapies.

There is a broad agreement that psychosocial treatments should be delivered to patients with schizophrenia and comorbid substance abuse. But there is still limited evidence that interventions used in people with addiction, for instance MI, are

efficacious in this special population. Most randomised controlled studies demonstrated only a slight advantage of these techniques compared to treatment as usual. In consequence to this, there is an increasing need to develop more effective treatment approaches, probably combining various psychosocial and pharmacological strategies. In addition to manualized treatment programs which may be a profound support for therapists and clients, more individualized approaches are needed.

In general, integrated treatment involves a flexible combination of treatments from the mental health and addiction fields to cover the needs of patients with dual diagnoses. Integrated programs require mental health staff to coordinate a range of approaches, such as detoxification, medication management, CBT, and MI and others. This may not feasible in several institutions due to limited resources and the absence of well-defined guidelines.

There is an increasing need to proceed researching the pathophysiological background of this comorbidity to develop new treatment approaches. The inside into the pathomechanisms of the endocannabinoid system (eCS) may also help to find innovative treatment strategies in schizophrenia without substance abuse. One of the potential new candidates with antipsychoptic properties related to the eCS is cannabidiol (CBD). Although Δ9-THC is commonly accepted as the main factor responsible for the effects of cannabis, several reports have demonstrated that other components of the plant influence its pharmacological activity. One of these components is CBD, which may constitute up to 40% of cannabis extracts and is devoid of the typical psychological effects of cannabis in humans [221]. In first case series CBD seems to be a safe and well-tolerated alternative treatment for schizophrenia compared to conventional and second generation antipsychotics.

In conclusion, the comorbidity of substance use disorders is common in patients with schizophrenia and causes serious consequences, including deterioration of psychiatric symptoms, medical problems, homelessness, legal problems, social isolation and reduced quality of life. There are some programs and integrated psychosocial treatment approaches available for this population. Although evidence is limited there exists at least case-based knowledge to guide the selection and management of pharmacological interventions. However, there are organizational barriers to systematically disseminating and implementing evidence-based interventions including fragmented services, and a lack of training among the front-line treatment providers. Coordinated efforts are necessary to provide optimal care for this vulnerable population. There is a need to implement changes in training and systems, as well as a need for new research initiatives to address gaps in our understanding of the clinical issues in this area.

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Chapter 16
Suicidality and Outcome in Schizophrenia Patients

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Abstract Almost half of all patients suffering from schizophrenia attempt suicide during their life emphasizing the dramatic impact of suicidality in schizophrenia illness. Today, several theoretical and biological models have been proposed to enhance the understanding of suicidality in schizophrenia patients in order to develop specific treatment strategies. A serotonergic dysfunction seems to be the underlying pathophysiological condition, imaging studies further suggest a gray matter density reduction in the temporal lobe of suicidal schizophrenia patients. This book chapter describes risk factors of suicidal action in schizophrenia patients with focus on the relationship between suicidality and outcome in this patient population. Among the most prominent risk factors of suicidality in schizophrenia are a younger age, male gender, depressive symptoms, insight into illness, non-adherence to treatment and the development of side effects. Today it is still unclear if suicidality affects response to treatment, for recently published studies were not able to detect a significant association between suicidality and predefined outcome criteria. However, suicidal patients seem to be significantly impaired through depressive symptoms, with a reduced functioning level and a greater vulnerability to side effects suggesting an association between suicidality and the course of the illness and its outcome. Different measuring instruments are introduced and clinical implications are discussed. Current treatment recommendations to reduce the risk of suicidality are furthermore reviewed in order to provide a better knowledge basis for clinicians and care providers.

Keywords Suicidality · Schizophrenia · Outcome · Influencing variables · Clinical implications

Abbreviations

EPS	Extrapyramidal side effects
GAF	Global assessment of functioning scale

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HAMD	Hamilton depression rating scale
PANSS	Positive and negative syndrome scale
SOFAS	Social and occupational functioning scale
UKU	Udvalg for Klinske Undersogelser side effect rating scale

Introduction

Suicide is among the leading causes of death worldwide and one of the three leading causes of death in people under 35 years of age [1]. Those suffering from schizophrenia are particularly at risk of dying by suicide for this is the leading cause of premature death in this patient population [2]. Suicidality in schizophrenia patients was already described by Bleuler as "the most serious of all schizophrenia symptoms" [3] and is still an enormous clinical challenge today. Approximately 50% of patients suffering from schizophrenia attempt suicide at some time in their life and almost 1 in 10 schizophrenic patients dies from suicide [4]. By the first treatment contact 15–26% have made at least one suicide attempt and almost as many patients at least one more during the first year of treatment [5]. Despite the considerable improvement in the treatment of schizophrenia suicidality remains a substantial burden for patients, their families, caregivers and society [6].

A number of theoretical models have been proposed in the literature in order to provide a better understanding of suicidal behaviour in schizophrenia as well as to generally understand the underlying mechanisms of suicidality [7]. Among those theoretical models are the Three Elements model setting up risk factors of predisposing factors, potentiating factors and suicidal threshold [8] or the so called Cubic model where external events, unmet psychological needs and the patient's distress are focused on [9].

Besides researching theoretical aspects of suicidality in schizophrenia, studies have tried to identify risk factors of suicidal behaviour that would not only help to reduce the mortality associated with suicidality but permit a more rational allocation of resources for treatment [10]. Lately, to add data to the growing body of research in this field, studies specifically examining the relationship of suicidal behaviour with response to treatment and the subsequent course of the illness were published [11]. Such studies are important, for the proof of a significant influence of suicidality on the patient's outcome might accelerate the development of specific treatment strategies.

Great effort has been made in setting up such treatment concepts in order to reduce suicidality and with it the mortality in schizophrenia patients with an emphasis on examining the role of atypical antipsychotics and their effect of treatment on suicidal behaviour [12]. Besides, the role of psychotherapeutic approaches and strengthening of resilience factors in suicide interventions have come into focus of research in the least years [13].

Based on the fact that only very few guidelines are available specifically addressing suicidality in schizophrenia this book chapter wants to provide an overview of current research data and their deriving clinical implications with focus on the latest advances regarding the relationship of suicidality and outcome.

Suicidality in Schizophrenia

Biological Aspects of Suicidality in Schizophrenia

Generally, a dysfunction of the serotonergic system is probably the most studied biological parameter in terms of suicidality. Lower concentrations of acid 5-hydroxyindoleacetic acid (5-HIAA) were found in the cerebrospinal fluid (CSF) of schizophrenia patients similar to other psychiatric illnesses [14]. Also, when assessing neuroendocrine tests and examining the prolactin response to a specific serotonin releaser and uptake inhibitor (fenfluramine, FEN) a significantly lower prolactin response was found in suicidal schizophrenia patients compared to the patients without such a psychiatric history [15] underlining the influence of the serotonergic system on suicidality in schizophrenia patients.

Genetics

Given the association between the serotonin system and suicidality in schizophrenia patients several genetic studies have focused on examining genetic polymorphisms of the serotonergic system. Shen et al., for example, analysed the relationship between the serotonin transporter protein (5-HHT) gene and suicidal behaviour, yet without finding a significant difference between suicidal and non-suicidal schizophrenia patients in terms of the intron 2 variable number tandem repeat polymorphism and the 5-HTT gene-linked polymorphic region, nor the haplotype frequencies of this gene [16]. A significant difference in the Serotonin Transporter Linked Promotor Region (5-HTTLPR) polymorphism, however, was reported when comparing patients with a first episode of suicidal behaviour and those with recurrent suicidality.

Other authors focussed on the serotonin synthesizing enzymes, namely the tryptophan hydroxylase isoform 2 (TPH2) again finding no significant association between the –473T>A (rs 11178997) and –8,396G>C (rs 4131347) polymorphisms of the TPH2 gene and completed suicide in patients with major psychosis (bipolar disorder or schizophrenia) [17].

The catechol-O-methyltransferase (COMT) enzyme was also investigated in schizophrenia and schizoaffective patients with suicide attempts [18]. The COMT L allele was reported to be more frequent in patients with an attempted violent suicide. The result reached statistical significance in males only. The authors concluded that their findings suggest that catecholaminergic alterations may contribute to suicidality and suicide attempts in this patient population [18].

Imaging Data

The first study investigating structural changes associated to suicidal behaviour in schizophrenia patients was only recently published by Aguilar et al. [19].

The scarcity of knowledge regarding neurobiological mechanisms as well as the heterogeneity of suicidal ideas especially in schizophrenia patients might have contributed to the slowed down research in this field. The authors performed a whole-brain magnetic resonance voxel-based morphometric examination in 37 male schizophrenia patients with 13 patients having attempted suicide. A significant gray matter density reduction in the left superior temporal lobe and in the left orbitofrontal cortex was found in the patients who had attempted suicide compared to the non-suicidal patients [19]. Despite several limitations of this study such as the small sample size and lack of a control group the results suggest structural differences in key cerebral areas.

The rather small number of studies examining potential neurobiological changes in schizophrenia patients suffering from suicidality points out the need for further research. This is even more highlighted when discussing that suicidality in schizophrenia might be an independent endophenotype [20]. Especially genetic and imaging studies can considerably contribute to a better understanding of the underlying biological mechanisms of suicidal behaviour in schizophrenia which might result in specific therapeutic consequences improving the course of the illness and mortality rates of this patient population.

Correlates of Suicidality in Schizophrenia

The identification and recognition of risk factors for suicidality and suicide in schizophrenia is a major element of prediction and prevention even though the individual suicide can most often not be predicted [21]. Such efforts are especially important in patients with schizophrenia because suicidal ideas are less often communicated [22]. Several studies were able to show that a high percentage of schizophrenia patients dying by suicide were seen by an apparently unsuspecting clinician several days prior to the suicide [23]. Generally, one can differentiate between suicide risk factors of all kinds of clinical populations and those unique to schizophrenia [2]. In the following, the most often reported variables associated with

Table 16.1 Risk factors of suicidal ideation, suicidal behavior and suicide attempts (this is not a full list of risk factors, but a collection of the consistent factors associated with suicidality in schizophrenia)

Risk factors		
Sociodemographic factors	Clinical factors and psychopathology	Treatment related factors
Male gender	Non-adherence	Side effects
Younger age	Substance use	No antipsychotic treatment
Being unemployed	Admission to or discharge from hospital	
Being unmarried	Depressive symptoms	
Living alone	Awareness of symptoms	

a higher risk for suicide in schizophrenia patients will be reported about. Table 16.1 shows the above discussed risk factors consistently associated with suicidality in schizophrenia patients.

Sociodemographic Variables

Younger age and male gender have most often been associated with suicidal actions in schizophrenia patients [24, 25]. Regarding the well documented association between younger age and higher risk of suicide is has been suggested that the effect of age disappears when other variables are controlled for, especially the variable of the duration of illness [10]. Typically, when attempting suicide schizophrenia patients are unemployed and unmarried [25] underlining the importance of rehabilitation and social working programs. Regarding the potential relationship between the patient's ethnicity and suicidality white race was repeatedly found to be a risk factor of committing suicide in schizophrenia patients [24, 26].

Clinical and Course Related Variables

One of the strongest and best researched predictors of suicide in schizophrenia is a previous suicide attempt in the patient's psychiatric history [27]. The suicide history of the patient's family also seems to play a significant role for the patient's risk to commit suicide [27]. Examining suicide victims between 1989 and 1998 Kreyenbuhl et al. [28] compared those victims with and those without schizophrenia regarding clinical and sociodemographic variables. They found patients with schizophrenia most frequently to jump from a height compared to suicide victims not suffering from schizophrenia [28]. Some studies suggested that patients with a paranoid subtype were at much higher risk of suicide compared to those with a deficit subtype [29], however controlled studies are still standing out.

In terms of when in the illness the risk of suicide is the greatest new data suggest that the risk of suicide in patients with schizophrenia continues throughout the course of the disease rather than being greatest in the first decade after onset of schizophrenia [30]. In a very recently published follow-up study of first-episode patients Robinson et al. examined 413 schizophrenia patients for more than 7 years [31]. First of all, the authors reported a very high rate of suicide attempts and a remaining elevated risk of suicide attempts for at least 7 years following commencement of treatment.

In relation to the question of when in their psychiatric care do schizophrenia patients attempt suicide the highest risk for completed suicide was found to occur during or soon after hospitalization [32]. The great majority of these suicide attempts do not occur on the ward, but in the grounds or the community when the patients is on weekend leave or absent without leave. The first and the last week of the hospitalization phase were furthermore reported to be particularly vulnerable periods for risk of suicide similar to the first months after the discharge from hospital [10] which has also been reported for affective disorders.

Psychopathological Variables

Depressive symptoms have been prominently associated with suicidality in schizophrenia [33–34]. It is believed that depressive mood and loss of interest might lead to demoralization in turn causing thoughts of hopelessness and dying [35]. These depressive symptoms in schizophrenia patients might be part of the core pathology or of pharmacogenic or akinetic origin. The importance of depressive symptoms especially regarding the severity of illness is also highlighted by studies on genetic polymorphisms and depressive symptoms in psychotic disorders [36]. Acosta et al. even propose a depressive subtype of suicidal patients suggesting a different management approach in each case and thereby fostering the adoption of appropriate preventive measures against subsequent suicidal behavior [37]. Also, hopelessness and self-reported distress were suggested to be associated with risk of suicide in this patient population [38]. In line with this are reports identifying loss of faith in the treatment as well as a realistic awareness of the illness often accompanied by depressive symptoms as distinct suicide risk factors [2].

The relationship between negative symptoms and suicide risk in schizophrenia patients has not been established yet for some studies suggest that negative symptoms are related to a lower risk of suicide [39], whereas others reported the exact opposite [11].

It has been thought for long that hallucinations and delusions are specific risk factors for suicide in schizophrenia [40]. The patient hearing voices telling him to harm himself have for long been thought to be notably responsible for suicidality in schizophrenia. Also, the tendency for irrational thinking and behavior when positive symptoms are present have been held responsible for suicidality [41]. However, data on this topic is somewhat inconsistent and newer studies were able to demonstrate the importance of depressive symptoms in terms of suicidality in schizophrenia [42].

Treatment Related Variables

Suffering from side effects was found to be a significant suicide risk factor in schizophrenia patients emphasizing the importance of a reduction of side effects in this patient population. Interestingly, when recently comparing suicide risk factors in schizophrenia and depressed patients a significant association between side effects and suicidality was only found in the schizophrenia patient subgroup suggesting that this patient group might be particularly vulnerable for side effects distressing the patients [43]. The subjective distress caused by extrapyramidal side effects (EPS) is widely reported [44]. Mainly akathisia, one of the most common EPS, has been associated with dysphoria and suicidality in case reports and pilot studies as well as review reports [45]. In a larger study, however, Hansen et al. examined 86 schizophrenia patients regarding the link between akathisia and suicidality and could not find a significant relationship at any assessment time point [44]. On the other side, in a naturalistic study examining over 200 schizophrenia patients,

the ones suffering from suicidality at admission were significantly more likely to develop EPS despite being treated with mainly atypical antipsychotics which are known to cause less stigmatizing side effects [11]. Given these contradictory results the need for larger and controlled trials is underlined to further examine the suicide risk of side effects in schizophrenia patients.

Measuring Suicidality in Schizophrenia Patients

High-quality suicide risk assessment tools are important instruments for care givers and clinicians in order to prevent suicide. In their review on suicide rating scales in schizophrenia Preston and Hansen underline the fact that not until recently specific scales designed for patients with schizophrenia at risk of suicide were largely unavailable [46]. They carried out a literature search using Medline and Psych-INFO databases and reported of mainly 3 different rating scales specifically assessing suicidality in this patient population: 1. The Schizophrenia Suicide Risk Scale (SSRS), 2. Scale for Suicide Ideation/Self-Report Version of the Beck Scale for Suicidal Ideation (BSI), 3. The InterSePT Scale for Suicidal Thinking (ISST).

The first listed scale, namely the SSRS, was found to have low sensitivity and might therefore not be a practical screening instrument for suicide risk in schizophrenia [47]. However, there were several flaws and incomplete data in the study proposing the SSRS so that future studies with more complete data, more representative subjects and a larger sample size might help to contribute to show that the scale has better sensitivity and specificity than thought before [46].

Already in the late 1970s Beck, Kovacs and Weissman developed a 19-item clinical rating scale to evaluate the severity of suicidal ideation called the Scale for Suicide Ideation (SSI) which was found to be a significant predictor of future committed suicides [48]. A handicap of the scale is that it has to be completed by a trained rater during a semi-structure interview. Therefore, Beck and Steer developed a self-report version of the SSI which is called the Beck Scale for Suicide Ideation (BSI) [49]. Using this self-report measure a patient is asked to read 19 groups of statements and to select the statement in each group that best describes his feelings. Pinninti et al. were the first to examine the BSI in schizophrenia patients [50]. They found the BSI total score to be positively correlated with having ever attempted suicide concurrently classifying 28% of the 130 patients with completed ratings to be suicide ideators. However, given the fact that not only schizophrenia, but also schizoaffective and bipolar patients with a comorbid DSM-IV Axis I disorder were included and that only hospitalized patients were examined the results' generalizability might be limited [50].

The InterSePT scale was developed for the use in the corresponding study to assess the severity of suicidal behaviour in the InterSePT clinical trial [51]. This scale derives from the BSI but deleted redundant items as well as items poorly correlating with the total score and with factor analysis. This scale was found to have good psychometric properties and satisfactory interrater reliability [52]. Current

literature leaves little doubt that this scale is a well made attempt to rate suicidality in schizophrenia patients. In their review, Preston and Hansen conclude that the ISST is the only suicide rating scale at this point which comes up to reasonable expectations of such an instrument [46].

Lately, the Columbia Classification Algorithm of Suicide Assessment (C-CASA), a rating method not specifically developed for schizophrenia patients, but approved and proposed as a standard measure to evaluate suicidality by the U.S. Food and Drug Administration (FDA) was found to be robust with satisfying reliability [53]. Its use in schizophrenia patients has to be examined and analysed in future studies.

Suicidality in Schizophrenia Patients and Outcome

Given the substantial burden of suicidality for schizophrenia patients one could assume that patients suffering from suicidality might have a less favourable course of the illness compared to patients not suffering from suicidal ideas or attempts. Surprisingly, this topic has not been researched very well. One explanation for this might be that patients with suicidality are among the most frequently excluded patients from clinical trials, especially effectiveness studies [54]. Just recently, Boter et al. addressed this problem in their publication on the generalizability of study results in first-episode schizophrenia patients based on data deriving form the European First Episode Schizophrenia Trial (EUFEST) [55]. In order to address this problem the authors compared patients suffering from suicidality as well as substance use with those not suffering from these comorbidities. Baseline demographic and clinical characteristics including follow-up data were examined. The comorbid patients were found to be younger, to be more likely male, less likely to be married with fewer years of education and higher levels of depression, however, most of these differences were explained by substance use, but not suicidality [55]. The small number of patients with suicidality analysed might contribute to this result. But despite the rather small number of suicidal participants, the authors were able to show that the suicidal patients have a significantly shorter time to rehospitalisation concurrently demonstrating higher scores of depression which might indicate a poorer outcome in this patient population.

Another study by Emsley et al. examining first-episode patients and their outcome considering suicidality as a potential influencing variable of the patient's outcome failed to find a significant association between suicidality and the chance to achieve remission [56]. 462 patients were examined within this long-term randomized, double-blinded trial of risperidone and haloperidol over 2–4 years. Remission was defined according to the Remission in Schizophrenia Working Group as a score of less than mild symptoms in 8 core items of the Positive and Negative Syndrome Scale (PANSS) for at least 6 months. 70% of the patients were found to have a reduction to mild levels of key symptoms as measured by the PANSS whereas only 23.6% met the remission criteria [56]. Suicidality was among the 4 variables (suicidality/neurocognitive scores/BMI/treatment group) that did not show a

significant difference between remitters and non-remitters. A possible explanation proposed by the authors was the rather high discontinuation rate so that the trial might not have had enough power to detect differences between remitters and non remitters [56].

There is only one naturalistic study examining the linear association between suicidality and outcome specifically focussing on the relationship between suicidality and response and remission at the patient's discharge from hospital. In this naturalistic trial Schennach-Wolff et al. evaluated 339 patients during their time of hospitalization finding 22% of the patients to be suicidal at admission [11]. The suicidal patients suffered from significantly more negative and depressive symptoms concurrently developing significantly more side effects. Interestingly, despite these significant differences the suicidal and non-suicidal patients did not differ significantly in terms of achieving response and remission at discharge as well as regarding time to response and remission [11]. The authors discuss that this might be due to the pre-defined outcome criteria of response and remission. The suicidal and non-suicidal patients both improved significantly in the total score of the PANSS so that the response definition of a 20% PANSS total score improvement could be easily reached also by the suicidal patients. Besides, the two patient subgroups did not significantly differ in the PANSS total score at discharge, the time point of assessing response and remission. The fact that the applied consensus remission criteria proposed by the Remission in Schizophrenia Working Group does not consider suicidal symptoms might have further contributed to their results [11]. Still, the authors concluded that given the burden of negative and depressive symptoms as well as side effects the suicidal patients seem to be impaired regarding the long-term course of the illness.

In line with this are several research reports finding variables consistently associated with a worse outcome, such as negative symptoms, non-adherence or substance use to be significantly associated with suicidality. This does not directly implicate that in turn suicidality leads to worse outcome, however, it suggests an association between suicidality and outcome in what way whatsoever. Novick et al. evaluated predictors and clinical consequences of non-adherence in schizophrenia outpatients who were treated within the observational European Schizophrenia Outpatients Health Outcomes (SOHO) study [57]. They found non-adherence to be significantly associated with an increased risk of suicide attempts and in turn non-adherence to be associated with a range of poorer long-term outcomes [57]. When comparing an early intervention service for first-episode schizophrenia patients with treatment as usual in a standard community mental health team Agius et al. found less suicide attempts to be associated with a generally more favorable outcome in the patient group with the special psychosis service [58]. Adair et al. assessed the continuity of care and health outcome in patients with severe mental illness and reported higher levels of observer-rated continuity to be associated with no suicidality [59].

Suicide attempts have furthermore been found to be a highly significant predictor of a greater rehospitalisation rate when examining predictors of relapse and rehospitalisation in 354 schizophrenia patients followed-up for 2 years [60] which is in line with the above discussed results of the EUFEST trial. The authors discussed that suicide attempts might be more frequent in severe forms of schizophrenia

characterized by a chronic course with increasing disability explaining the higher need of hospitalisations. However, this result underlines the fact that suicidality seems to significantly influence the patient's outcome. Significant differences between suicidal and non-suicidal patients were very recently demonstrated by Schennach-Wolff et al. [61] when examining the patient's psychopathology, depressive symptoms, functioning and side effects compared between suicidal and non-suicidal patients. Several significant differences were reported between the patient subgroups suggesting an influence of suicidality on the course of the illness and therefore on the patient's outcome [61]. The PANSS was used to describe the general psychopathological condition, the Hamilton Depression Rating Scale (HAMD) to evaluate depressive symptoms, the Global Assessment of Functioning Scale (GAF) and Social and Occupational Functioning Scale (SOFAS) scales to assess functioning and the UKU scale to examine side effects [61] (Figs. 16.1, 16.2, 16.3, 16.4, and 16.5).

In addition to a relationship between suicidality and symptomatic outcome, a significant association was also reported for suicidality and functional outcome. Within a naturalistic study 262 schizophrenia patients were examined predicting functional outcome defined via the Global Assessment of Functioning Scale, the Social and Occupational Functioning Scale and the Medical Outcomes Study – Short Form Health Survey [62]. Less suicidality was amongst others found to be a significant predictor of functional outcome.

Another aspect that should be mentioned in this context is the often described link between suicidality and the patient's insight. Insight in schizophrenia is considered to be a multidimensional concept and was found to be a risk factor of suicidal behaviour [63]. When evaluating the predictive potential of insight into illness in

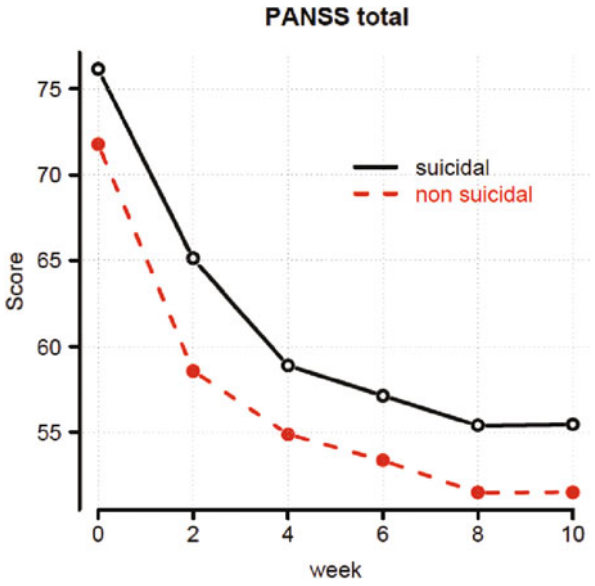

Fig. 16.1 Comparing the PANSS total score between suicidal and non suicidal schizophrenia patients; no significant difference could be observed between the two groups in the mean PANSS total scores at any assessment time-point

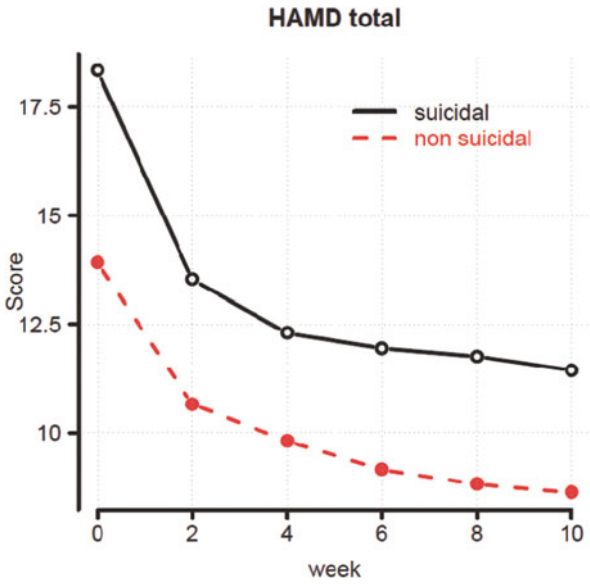

Fig. 16.2 Comparing the HAMD total score between suicidal and non suicidal schizophrenia patients; a significant difference could be observed between the two groups in the mean HAMD total scores throughout the course of treatment ($p < 0.0001$)

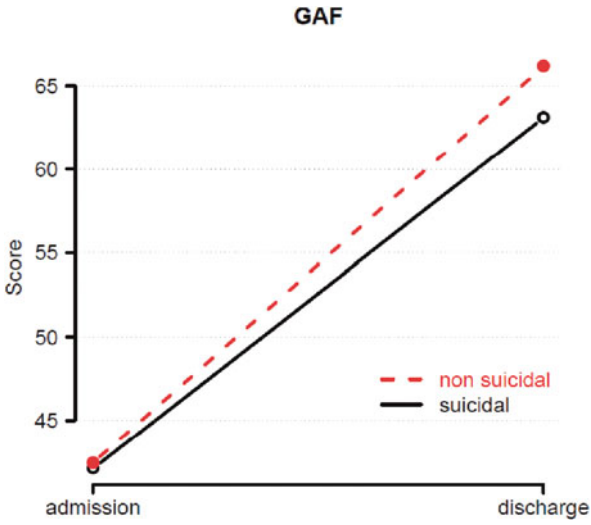

Fig. 16.3 Comparing the GAF score between suicidal and non suicidal schizophrenia patients; a significant difference could be observed between the two groups in the GAF score at discharge ($p = 0.0440$)

suicidal patients with psychosis Schwartz and Smith detected increased insight into illness to significantly heighten the patient's risk for suicidality [64]. It is believed that patients with greater insight develop a sense of hopelessness and demoralization leading to suicidal behavior [65]. In turn, insight has been found to be associated with relapse and readmission [63, 66] again suggesting that suicidality might also

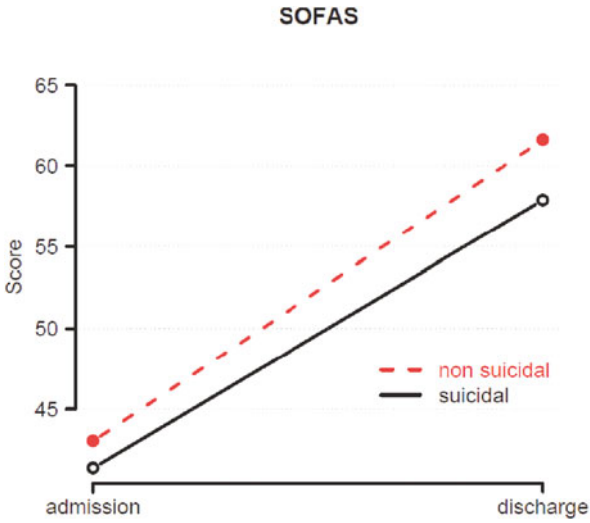

Fig. 16.4 Comparing the SOFAS score between suicidal and non suicidal schizophrenia patients; a significant difference could be observed between the two groups in the SOAFS score at discharge ($p = 0.0216$)

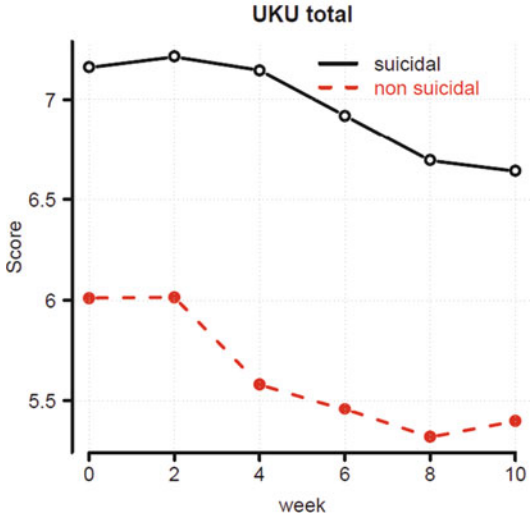

Fig. 16.5 Comparing the UKU total score between suicidal and non suicidal schizophrenia patients; a significant difference could be observed between the two groups in the UKU total score at discharge ($p = 0.0326$)

be associated with a worse outcome and course of the illness. Amador et al. examined insight and suicidality in 218 patients and reported that patients with recurrent suicidal thoughts were more aware of their schizophrenia symptoms. Consequently, schizophrenia patients with less insight seem to have a better quality of life with higher self-esteem. This is in line with reports of healthy controls [67] as well as depressed patients finding a certain degree of denial of reality to be linked to better mood.

Clinical Implications and Treatment of Suicidality in Schizophrenia Patients

Pharmacological Treatment

Great effort has been made to evaluate the antisuicide effects of pharmacological treatment in patients with schizophrenia. Research studies suggest that suicide in patients with schizophrenia occurs much more in those patients not being adequately treated or not being treated at all [68]. Results regarding an association between suicide risk and the antipsychotic dosage apply vary. Some studies were able to show a relationship between lower doses and suicide, whereas others found higher antipsychotic dosages to be associated with suicide [69]. The conclusion of a linear relationship between suicide and antipsychotic dose is therefore not possible.

Lately, Aguilar and Siris reviewed the potential influences of antipsychotic drugs in schizophrenia by performing a MEDLINE search for articles written in English and published between 1964 and 2006 [69]. The authors pointed out several inconsistencies among the studies as well as methodological difficulties making a final conclusion on this topic impossible. Generally, atypical antipsychotics were found to possibly have a better potential for preventing suicide in schizophrenia patients, however, no clear guidance can be provided regarding specific antipsychotic agents [69]. The strongest evidence for reducing suicidality was shown for clozapine having a clinically relevant advantage over typical as well as atypical antipsychotics. Another meta-analysis by Hennen and Baldessarini also found a substantially lower risk of suicidal behaviour and for completed suicides for clozapine [70].

The first study overcoming methodological limitations of the past by applying a prospective study design and a large patient sample was the InterSePT, a randomized, open-label trial including 980 patients with schizophrenia or schizoaffective disorder [71]. Patients with at least one suicide attempt during the 3 years prior to the inclusion into the study or with current suicidality were examined comparing treatment with olanzapine and clozapine. The study's primary outcome measure was the time to a suicide attempt as well as a hospitalization to prevent suicide. A blind, independent, expert so called Suicide Monitoring Board determined whether or not the potential endpoint met these criteria [71]. Clozapine was found to be superior to olanzapine despite no difference in terms of the overall efficacy reducing the patient's general psychopathology [71].

There is a widespread use of an augmentation with antidepressants in suicidal schizophrenia patients who are treated with antipsychotics [40]. It seems that schizophrenia patients who seem to benefit most from this strategy are the ones not floridly psychotic and presenting with a full syndromal presentation of depression. Also, in a recently published randomized controlled trial of citalopram as add-on treatment in schizophrenia and schizoaffective disorders citalopram showed a reduction of suicidal ideation, especially in those patients whose depressive symptoms responded to treatment [72].

Taken together, it is currently excepted that clozapine has a unique role in the treatment of suicidality in schizophrenia patients with most researchers and

clinicians accepting that clozapine has antisuicide effects [73]. Therefore, in patients suffering from schizophrenia with a serious suicide attempt in their psychiatric history or with a very high risk for such an attempt clozapine treatment should be initiated and maintained. In patients with prevalent depressive symptoms an additional treatment with antidepressants should be considered.

Non-pharmacological Treatment

Psychotherapeutic approaches in schizophrenia were found to require specific modifications of the standard technique. One approach suggested by Hogarty et al. is the so called Personal Therapy which begins soon after discharge and focuses on symptomatic stabilization and a satisfying therapeutic relationship [74]. Later on the patient's introspection and understanding of stressors and dysfunctional behaviour are the picked out central themes. Psychoeducational elements and relaxation training are furthermore incorporated. Generally, reality-orientated interventions such as social skills training, vocational rehabilitation and supportive employment are important in the prevention of suicide in patients suffering from schizophrenia [75]. Especially reality-orientated supportive therapies giving the patient the opportunity to talk about daily activities or difficulties regarding the medication were found to be of special importance. In a review of controlled trials of psychotherapy by Mueser and Berenbaum it was concluded that so called reality-orientated psychotherapy is superior to an insight- and dynamic-related focus [76]. Just recently, a positive self-appraisal in schizophrenia patients was found to improve the identification of individuals at high risk of suicidality thereby presenting an interesting and important target for suicide intervention [13].

Conclusions and Future Directions

Suicidality is a major burden for patients suffering from schizophrenia as well as for their relatives and care providers. Especially depressive symptoms have consistently been associated with suicidal ideation and actions suggesting a more radical treatment of this symptom domain in schizophrenia patients. Latest study results in this respect suggest satisfying tolerability of add-on antidepressants and a reduction of suicidal ideation through the add-on strategy. Today, no significant differences in predefined outcome criteria could be observed when comparing schizophrenia patients with and without suicidality. However, suicidal schizophrenia patients seem to suffer from significantly more psychopathological symptoms, featuring significant impairments in functioning concurrently developing significantly more side effects suggesting a worse course of the illness. Future studies are warranted examining clinical and biological factors at the same time to further improve the understanding of suicidality in schizophrenia patients and to develop more specific treatment strategies resulting in a reduction of the illness's mortality rate.

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Chapter 17
Religiousness/Spirituality and Schizophrenia: Implications for Treatment and Community Support

Jennifer A. Nolan, Rachel E. Dew, and Harold G. Koenig

Abstract Previous research into psychosis as it relates to religion or spirituality has focused on the phenomenon of religious delusion. Due to the prevalence of religious material in delusional systems, some psychiatrists may fear that all exposure to religion/spirituality conveys the risk of exacerbating psychosis. However, recent investigation reveals that for many psychotic patients, religion/spirituality offers solace, social support, and enhanced coping. Private religiousness/spirituality (i.e. prayer, beliefs, or a relationship to the divine) appears to be a prevalent method for coping with schizophrenia. Evidence also suggests that public religiousness (i.e. service attendance, Bible study groups) is helpful to some psychotic patients. Different styles of religious coping have been found to correlate with important health outcomes in the major psychoses, such as quality of life, medication adherence, substance abuse and suicide. If confirmed, this research may have clinical and public health implications. Mental health care providers may need to be trained to support religious coping among psychotic patients, rather than assuming it to be an irrelevant or possibly destabilizing force. Educational interventions may help religious groups to better accept and integrate individuals living with schizophrenia into their communities, thus enhancing social support for the severely mentally ill. This chapter will review the following topics: (1) the disabling and stigmatizing effects of severe mental illness, and the lack of adequate community support worldwide, in the context of limited available inpatient care; (2) the dearth of research characterizing relationships between religiousness/spirituality and severe mental illness, which exists in spite of the plethora of research on its relationship to depression, anxiety, substance abuse, and overall psychological well-being; (3) religious delusions in psychotic illness and concerns that exposure to religion may worsen psychosis; (4) the role of the cultural and religious context in determining how psychotic illness is understood; (5) review of past and current research on the relationship between

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religiousness/spirituality and health outcomes in the severely mentally ill; (6) directions for future research; and (7) potential implications of research for treatment and community interventions.

Keywords Religion · Spirituality · Schizophrenia

Abbreviations

HIV	human immunodeficiency virus
HIV/AIDS	human immunodeficiency virus/ acquired immune deficiency syndrome
CBT	cognitive-behavioral therapy
RCBT	religious-based cognitive-behavioural therapy
PCT	pastoral counselling therapy
MBSR	mindfulness-based stress reduction
fMRI	functional magnetic resonance imaging
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
CASA	National Center on Addiction and Substance Abuse
DSM	Diagnostic and Statistical Manual
CASH	Comprehensive Assessment of Symptoms and History
CASH-CS	Comprehensive Assessment of Symptoms and History an adapted culturally sensitive version
ECA	Epidemiologic Catchment Area
QOL	Quality of Life
WHOQOL-BREF	World Health Organization Quality of Life-BREF

Introduction and Background

This chapter will review research on the role of religious and spiritual beliefs and practices in living with schizophrenia. While a relatively large literature documents connections of religiousness/spirituality to less debilitating mental illnesses such as depression and anxiety, possible relationships between spirituality and severe mental conditions such as chronic psychosis are rarely examined. In the few studies conducted thus far, many sufferers of schizophrenia report that religious beliefs and practices play an integral role in living with the illness. On the other hand, religious delusions often characterize psychotic exacerbations. Understanding the role of religious and spiritual beliefs and practices among individuals living with schizophrenia may help to better inform treatment and community support initiatives.

In order to highlight the dire need for preexisting social institutions to contribute community support to those with schizophrenia, the authors will first review what is known about the critical lack of resources currently available to individuals living with severe mental illness. Schizophrenia is often associated with chronic

morbidity and disability, increased mortality, low quality of life and isolating social stigma [1–3].

The point prevalence of schizophrenia is approximately 0.5 percent; variation in this rate relates to such factors as illness definition, age distribution and geographic setting [4, 5]. Globally, schizophrenia is estimated to affect 26.3 million individuals [6]. Torrey [7] estimates that approximately 2.2 million Americans suffer from schizophrenia in any given year, about eight persons out of every 1,000, yet at least 40 percent are not being treated at any given time.

Kleinman [8] characterizes the plight of the severely mentally ill as fundamentally a moral problem and a failure of humanity. Within the United States, about one-quarter of the schizophrenic population lives in nursing homes, prisons, hospitals, shelters or on the streets [7]. In less wealthy countries, more than 75 percent of those living with serious mental or substance use disorders receive no care at all [9]. In sub-Saharan Africa, this figure may exceed 90 percent [10]. What little treatment is available in less wealthy countries may fall below minimum acceptable standards [11].

Media exposure in the mid-twentieth century sparked public interest on the inhumane conditions of U.S. state psychiatric hospitals. In response, a series of 2000 federally funded community mental health centers were planned to function as alternatives to state hospitals, yet due to funding issues far fewer were actually created [7, 12]. Those that exist are often underfunded. Consequently mass deinstitutionalization has left a large population of mentally ill persons with inadequate treatment, case management, housing, and rehabilitation resources.

Morrissey and Cuddeback [13] state that jails have essentially replaced state psychiatric hospitals as the last resort for management of the severely mentally ill, and that this group is nearly 50 percent more likely to be jailed than hospitalized. However correctional facilities often lack adequate treatment and services for the severely mentally ill [14]. The rate of schizophrenia among prisoners is almost five times higher than the general population [15]. Once released from jail or prison, individuals living with schizophrenia often have difficulty engaging in community mental health services; with little or no access to medications, transportation, financial or social support, they often become homeless. Moreover, individuals living with schizophrenia are at a much higher risk than those in the general population to be victims of violent crime [16].

The cost of schizophrenia in the US in 1990 was estimated to be $32.5 billion [17]. This figure incorporates both direct costs of treatment and hospitalization, and indirect costs such as lost wages. A review of all existing international estimates on the economic costs of schizophrenia found that the disease typically accounts for 1.5 to 3 percent of total national health care expenditures [18]. This illness also ranks among the ten leading causes of disability worldwide, despite its relatively low prevalence [6]. In less wealthy countries, it is not uncommon for individuals living with severe mental illness to be hidden at home by family members due to stigma. This creates a heavy burden on families already struggling to meet their own basic needs [19].

There is a serious lack of mental health professionals in less wealthy countries. Saxena et al. [20] report that low-income countries have a median of 0.05

psychiatrists and 0.16 psychiatric nurses per 100,000 people, while high-income countries have a ratio that is 200 times higher. Some African nations have been documented to have only one psychiatrist in the entire country [21]. In addition, treatment in these nations is limited by lack of access to psychotropic medications. The supply is often irregular and/or limited to certain regions [20]. It has been argued that these conditions constitute a human rights emergency, and that the lack of care available to the severely mentally ill is a moral failure of mankind [8]. To address this crisis in the face of deinstitutionalization, acute and continuing care services within local communities must be developed [11].

Lack of available treatment and basic resources for those with schizophrenia is a serious and global problem. The following sections of this chapter will examine the research on religion and spirituality in relation to living with severe mental illness; this research may illuminate how faith-based organizations may assist in decreasing the suffering, stigma and poor quality of life of the severely mentally ill.

Religion and Mental Health

Religious or spiritual beliefs and practices have been more fully considered within the field of psychiatry within the last two decades. Prior to the 1990s, little mental health research addressed religiosity; reasons for this deficit may include: the belief that religion or spirituality are part of the pathology of mental illness [22–24]; lack of interest in or education about religion and spirituality among mental health professionals [23, 25]; and possible competition for clients, as both clergy and mental health professionals are experts on human suffering [24, 26, 27].

Since the 1990s, associations between religiousness and health, including mental and physical health, have been explicitly tested. Hufford [28] argues that public demand for the reconciliation of religion/spirituality and health care has grown partly because of patients' dissatisfaction with medical technology's ability to deliver the highest quality of life in treatment and recovery. This relatively new field has highlighted religiousness/spirituality as very important in the lives of many medical and psychiatric patients. This section provides a review of selected studies on relationships between religiousness and mental health outcomes. We emphasize that in no way is this review exhaustive; selected studies are highlighted to simply illustrate evidence for the relationship. As this is a relatively new field of research, multiple conceptual and measurement issues remain under debate in the literature. Subsequent to this review and critique, hypothesized pathways underlying the relationship between religion and health are summarized.

Empirical studies since the nineteenth century have found positive associations between religion and mental health [29–31]. The majority of these studies examined the link indirectly, considering religious variables only as potential confounders or interacting variables. Such findings were often overlooked, obscured in tables without comment. New studies, reviews, and meta-analyses over the last two decades have specifically explored associations of religiousness/spirituality to mental and physical health outcomes [28–34]. This new body of research documents cross-sectional and longitudinal relationships of religiousness

to important positive – and, less frequently, negative – health outcomes. Examples of outcomes explored in this field include HIV/AIDS, coronary artery disease, hypertension, overall mortality, depression, post-traumatic stress disorder, substance abuse, antisocial behavior, and coping with various disease states such as cancer and congestive heart failure [30].

Conceptualization of Religion and Spirituality

'Religiousness' and 'spirituality' are elusive and loaded terms, and may be operationalized and measured in many different ways. Most researchers distinguish between 'religion' and 'spirituality.' Koenig et al. [30] and Larson et al. [35] state that there is both difficulty in reaching consensus about the distinctiveness of these concepts and acknowledgement of conceptual overlap between religion and spirituality. 'Religion' derives from the Latin root *religio*, and is typically conceptualized as a system of traditional beliefs, attitudes, and practices oriented toward the sacred [35]. The word 'spirituality' derives from the Latin root *spiritus*, which may be interpreted as 'breath' or 'life.' Spirituality is typically conceptualized as including elements of religion but more generally denotes views and behaviors that express relatedness to something greater than the self. Zinnbauer et al. [36] found that most individuals (74%) describe themselves as *both* religious and spiritual based on interviews with a diverse sample of 346 individuals.

Many researchers conceptualize religion and spirituality as multifaceted. Variables commonly studied in this field include: religious beliefs and practices, attitudes, values, development, orientation, commitment, involvement, spirituality and mysticism, forgiveness, fundamentalism, intrinsic and extrinsic religiosity, images of God, spiritual maturity, affiliation, biographical history, motivation, and attitudes toward death. Religious coping is a construct that denotes use of doctrinal, social, or behavioural aspects of religion or spirituality to cope with life's challenges. Another important emerging concept is that of religious or spiritual struggle [37], measured with such items as "wondered whether God had abandoned me" or "wondered whether God was punishing me because of my lack of faith" (pp. 522–523) [38]. Nonetheless, because spirituality is difficult to measure, most studies use religious indicators such as religious service attendance as a proxy for spirituality.

Religion and Mental Health Outcomes

The following section provides a summary review of the literature on religiousness and spirituality in relation to mental health outcomes such as depression, anxiety, suicide and substance abuse.

A comprehensive study by Kendler and colleagues [39] sought associations among the multidimensional aspects of religion measured by seven religiosity factors and the lifetime risk for nine psychiatric syndromes among a sample of 2,616 individuals drawn from a general population registry. The nine syndromes were divided into five internalizing disorders: major depression, generalized anxiety

disorder, phobia, panic disorder, and bulimia nervosa. The four externalizing disorders included nicotine, alcohol, and drug abuse or dependence, and adult antisocial behaviour. The factors of social religiosity and thankfulness were found to be protective against lifetime risk for both internalizing and externalizing disorders. The factors of general religiosity, an involved God, forgiveness, and God as judge, were found to be protective against externalizing disorders and lack of vengefulness was found to be protective against internalizing disorders. Overall religiosity was found to be a "complex and multidimentional construct with substantial associations with lifetime psychopathology" (p. 496) [39].

Depression

An inverse relationship between religious participation and depression has been found in most studies. Koenig et al. [30] reviewed over 100 quantitative studies on the relationship between religious involvement and depression and found that two-thirds of the cross-sectional studies reported lower rates of depression with higher religious involvement. Concomitantly, individuals with higher levels of religious participation were less likely to be diagnosed with depressive disorders. Only four studies found being religious was associated with significantly more depression, and 34 studies found no association. Longitudinal studies reported similar findings to those of the cross-sectional studies, with over two-thirds (15 out of the 22) of studies finding that greater religiousness at baseline was predictive of fewer depression symptoms or faster remission of symptoms at follow-up.

Several studies since Koenig's review was published have supported the findings. A national cross-sectional Canadian study by Baetz et al. [40] on spiritual and religious involvement that controlled for demographic, social and health variables found that those with higher levels of attendance reported fewer depressive symptoms. However, those who stated that spiritual values or faith were important, or who perceived themselves to be spiritual or religious, reported higher levels of depressive symptoms. The authors note that perhaps the more depressed have turned to religion and spirituality to help to cope with their depression. A study by Smith et al. [32] conducted a meta-analysis of 147 studies comprising a total of almost 100,000 subjects. The average inverse correlation between religious involvement and depression was −0.10, increasing to −0.15 among samples of stressed populations. This correlation is of similar magnitude to the effect of gender, a commonly recognized factor influencing the prevalence of depression.

In addition to observational studies, some researchers have attempted to incorporate religious and spiritual elements into treatments for depression. Koenig et al. [30] reviewed eight clinical trials. Five of the trials showed that those exposed to religious involvement recovered significantly faster than those not exposed or those exposed to a secular based therapy. Azhar and Varma [41] conducted a study on the effects of psychotherapy with a religious perspective compared to psychotherapy with no religious perspective. Sixty-four highly religious Muslim patients in Malaysia with dysthmia were randomly assigned to one of two groups. The control group had weekly supportive psychotherapy plus psychotropic medication, while the religious

psychotherapy exposure also included discussion of religious issues and prescription of religious practices, such as prayer and reading the Koran. Patients exposed to the additional religious psychotherapy showed more rapid improvement in their depressive symptoms; the difference was significant at three months but not at six months. Koenig and colleagues [30] state that although the results support the general hypothesis that religious involvement speeds recovery from depression, it is not clear whether these results come from a dose-effect relationship in psychotherapy, which holds that more treatment leads to greater improvement.

In a similar study, Propst et al. [42] randomly assigned 59 religious patients with depression to traditional secular cognitive-behavioral therapy (CBT) without religious content, religious-based cognitive-behavioural therapy (RCBT), ordinary pastoral counselling (PCT), and a no therapy wait-list control group. Patients exposed to the two religious interventions reported significantly lower post-treatment depression scores, but there were no significant differences among the treatment groups at three and 24 months follow-up. Surprisingly, nonreligious therapists achieved better results using RCBT than did religious therapists. As such, it appears that one does not have to be religious to deliver a religiously based intervention.

Koenig et al. [30] and Johnson and Ridley [43] explain that the rationale behind religious treatment approaches in psychotherapy is the principle of accommodation. This principle states that secular approaches to psychotherapy may be translated into the language of religious clients in order to improve compliance, satisfaction, understanding and mental health outcomes. Religious versions of standard cognitive-behavioural techniques such as cognitive restructuring and cognitive coping skills have been developed. Religious techniques including "biblical counterchallenges" and "scriptural justification for rational thinking" (p. 134) [30] are thought to be theoretically equivalent to standard cognitive-behavioural therapies, but more consonant with the worldview of religious clients. Accommodative forms of religious psychotherapy have also been developed with behavioural interventions such as prayer and religious imagery [44].

A recent clinical trial examined the effects of intercessory prayer on depression, anxiety, positive emotions and salivary cortisol levels [45]. Patients were randomized to receive weekly direct person-to-person prayer contact over six weeks ($n = 27$); control subjects received none ($n = 36$). Participants receiving the prayer intervention showed greater improvement in depression and anxiety, as well as increases in daily spiritual experiences and optimism. These differences were maintained at least one month after the intervention. However cortisol levels did not significantly differ between the two groups. Koenig et al. [30] states that additional research is needed to determine whether religious-accommodative psychotherapies differ from standard psychotherapies in long-term effectiveness.

Anxiety

Koenig and colleagues [30] conducted a systematic review of studies prior to 2000 and found that half (35 out of 69 studies) of the observational studies found significantly less anxiety or fear among the more religious; 24 studies reported

no association. Ten studies reported increased anxiety in the religious. However, Koenig notes these studies are cross-sectional and that anxiety is a strong motivator for religious activity; as such, cross-sectional studies may observe anxious subjects turning to religion to combat current anxiety. Among seven randomized control trials, six found that religious interventions in religious patients reduced anxiety levels more quickly than secular based interventions. Ellison et al. [46], using data from a nationally representative sample of US adults ($n = 921$), found that religious attendance and belief in an afterlife were inversely associated with feelings of anxiety and positively associated with feelings of tranquility, while prayer had no association. Other findings from Ellison's study found that strong beliefs about human sinfulness were associated with anxiety and prayer, and that belief in an afterlife buffered the adverse effects of poor health and financial decline on anxiety.

Mindfulness-based meditation therapy, related to Buddhist traditions, has been found to be effective for anxiety, depression and spiritual well-being among cancer patients [47]. Among those with social anxiety disorder, mindfulness-based stress reduction (MBSR) has been shown to improve anxiety, depression, and self-esteem [48]. Based on functional magnetic resonance imaging (fMRI) of socially-anxious subjects, MBSR may reduce emotional reactivity and enhance emotion regulation. In a randomized study by Koszycki et al. [49], both meditation-based stress reduction and cognitive behavior group therapy improved mood, functionality and quality of life among patients ($n = 53$) with social anxiety; however, the cognitive behavioral group therapy showed greater effects on social anxiety. In a review by Toneatto and Nguyen [50] on mindfulness-based stress reduction in a range of clinical populations, evidence for the beneficial effects in depression and anxiety was equivocal. The authors note that the risk of relapse after successfully treated depression does appear to be reduced by exposure to MBSR; thus it may be most useful as an adjunctive treatment.

Suicide

It is estimated that more than 90 percent of completed suicides occur in the context of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) psychiatric illnesses [51]. In systematic review of studies on the relationship between religion and suicide Koenig and colleagues [30] found that the majority (57 out of 68) of the studies documented fewer suicides or more negative attitudes toward suicide among the more religious. Nine studies showed no relation between religious variables and sucidality, and two revealed mixed results.

Rasic et al. [52] conducted a cross-sectional study utilizing a nationally representative Canadian sample ($n = 36, 984$) to examine the relationship between religious attendance and suicidal behavior. Religious attendance at least yearly was associated with decreased odds of suicide attempt after adjusting for sociodemographic factors and social supports; results were similar for those with a mental disorder. Likewise, in a study by Nisbet et al. [53] those 50 years and older who completed

suicide ($n = 584$) were less likely to have ever participated in religious activities. Interestingly, social contact did not reduce the likelihood of suicide.

The relationship between religiousness and decreased suicide attempts has been explained by Durkheim's [54] idea that spiritual commitment provides a source of meaning and order in the world. Based on a review of the literature, Gearing and Lizardi [55] state that the protective role of religion is found across major religious denominations. Beyond proscription of suicide itself, many religions do not allow behaviors such as substance abuse, which have an established relationship to suicide [56].

Substance Abuse

In a review of over 100 studies, Koenig and colleagues [30] found significantly less substance use and abuse among the more religious in about 90 percent of the studies. Koenig notes that most of these studies were conducted among high school or college students, who are just starting to establish patterns of alcohol and drug use. The National Center on Addiction and Substance Abuse (CASA) reported based on the analysis of three national surveys that adults who did not consider religion very important were 1.5 times more likely to use alcohol and cigarettes, three times more likely to binge drink, four times more likely to use illicit drugs other than marijuana and six times more likely to use marijuana, compared to adults who considered religion important [57]. Similar results are reported for the relationship between religious attendance and substance abuse. In addition, people who received both professional treatment and attended spirituality-based support programs (such as Alcoholics Anonymous or Narcotics Anonymous) were far more likely to remain sober than if they received only professional treatment [57]. The report recommends a better understanding by clergy of the disease of addiction and a better appreciation by clinicians of the role of religion and spirituality for prevention and treatment of substance abuse. However, Miller et al. [58] conducted two controlled trials ($n = 60$; 40) on spiritual direction as an adjunct therapy to addiction treatment, finding in both trials that spiritual guidance had no effect on substance use outcomes.

In summary, systematic research published in the mental health literature has found that religious involvement has a generally positive relationship with mental health and better coping. It has been associated with less depression, suicide, anxiety and substance abuse, in diverse studies of medical, psychiatric and general populations. However, some forms of religiousness or spirituality may have a negative effect on mental health, especially among the emotionally vulnerable. Religious beliefs and practices may exacerbate neurotic tendencies, fears, guilt and possibly restrict life rather than enhance it. Religious beliefs may act as defense to avoid making necessary life changes. Thus Koenig [22] recommends that clinicians be cognizant of the religious and spiritual activities of their patients in order to discern whether the beliefs and practices may contribute to improved functioning or to the pathology.

Religion and Spirituality in Psychosis

Approximately 25 to 29 percent of schizophrenic patients and 15 to 22 percent of bipolar patients experience delusions with religious content [59]; the prevalence varies across time and culture. Cultures in which religion plays a more central role have a higher prevalence of delusions with religious content [60–62]. For example, the prevalence of religious delusions in schizophrenia has been reported to range from 7 percent in Japanese patients [63], to 21 percent in Germans and up to 80 percent in Afro-Carribbean populations [64].

A study by Drinnan and Lavender [65] found that religious delusions were influenced by personal and social experiences, such as early experiences within the family. It is important that clinicians have an understanding of the patient's cultural context in order to distinguish delusional material from what is actually part of the person's culturally appropriate belief system [61, 65].

Previous research has shown that the prevalence of religious delusions is influenced by cultural and political conditions over time. In an Egyptian study (n = 5,275) [62], the prevalence of religious delusions over a 22-year time period was observed to vary with the changing political and religious climate. From 1977 through 1986, during times of political and religious turmoil including the assassination of the president, the frequency of religious psychotic symptoms among Egyptians almost doubled. After four years of relatively low rates of religious symptoms, the frequencies again spiked in 1989 to 1990, coinciding with the outbreak of religiously influenced violence [62].

Kim and colleagues [66] studied schizophrenic patients from Seoul, Korea (n = 370), Korean-Chinese patients (n = 225) and Chinese patients from Yanbien, China (n = 176). Religious delusions were observed to be among the most sensitive to changes in the sociocultural and political climate. Korean patients reported the highest frequency of religiousness (38.7%) and also had the highest rate of religiously themed delusions (25.1%). Chinese and Korean-Chinese patients reported far lower rates of religiosity (0.6% and 1.3% respectively) and also had very low rates of religious delusions (0–1%).

Another study assessed records of delusional material among patients at the Bethlam Royal Hospital in London, England, comparing a set of records from 1853 to 1862 (n = 200) with another from 1950 to 1960 (n = 200) [67]. They found that the prevalence of religious delusions in the nineteenth century sample was three times that observed in the twentieth century sample. The authors propose that this may correlate to the relative importance of religion in British culture over time.

The specific content of religious delusions may be influenced by religion and culture. Tateyama et al. [63] compared the delusions of inpatients with schizophrenia in three countries, Japan (n = 324), Austria (n = 101) and Germany (n = 150). Religious themes of guilt/sin were more prevalent in the European countries, while in Japan the delusions of reference, such as being slandered, were more prevalent. The latter phenomenon may originate from the role that shame plays in the group oriented culture of Japan.

In a study by Rudaleviciene et al. [68] among 295 patients suffering from schizophrenia, about three-quarters reported delusions of persecution. The prevalence of delusions of persecution was lower in the group of persons for whom faith was personally important (73.4%) than in the atheistic group (86.7%). In another study of the same cohort, 63.3 percent reported religious delusions. The most frequent content was that women believed themselves to be saints and men believed themselves to be God. Based on multivariate analyses, religious content of delusions was not correlated to personal religiosity, but rather to marital status and education [69].

Religious and spiritual beliefs and practices may contribute to the problem of psychosis, or may promote positive coping and improved quality of life [70]. Fallot [71] points out that religion may be harmful to individuals regardless as to the presence of mental illness, contributing to feelings of guilt, unworthiness, stigmatization, manipulation, exploitation and victimization. A more specific way religious teachings may harm psychotic patients is through misinterpretation of scriptural teachings. Changes in abstract thought processes associated with schizophrenia have been associated with self-mutilation, such as removing the eye that has "offended" or command hallucinations which instruct a person to kill someone who is considered "evil" (p. 594) [71]. However, it may be that such impulses would have occurred whether or not the patient was exposed to religious teachings.

Intense religious experiences and religious conversions may trigger acute psychotic or manic symptoms among vulnerable individuals [72]. Likewise psychosis may initiate intense religious experiences or change in less traditional religious affiliations [73]. Huguelet and Mohr [24] state that at the clinical level, the temporal sequence of events and symptoms needs to be assessed, while at the population level more research is needed.

Diagnosing Delusions with Religious Content

Delusions are commonly experienced both in the general population and in the seriously mentally ill. Based on epidemiological studies, 10 to 28 percent of the general population without psychotic diagnoses have delusions, whereas the lifetime prevalence of true psychotic disorder is about one percent [5, 74, 75]. Siddle et al. [76] maintain that given the frequency religious delusions in the nonpsychotic general population, it is important that the presence of other psychotic symptoms be determined in order to reliably establish a diagnosis of schizophrenia.

Ng [77] states that psychiatrists are educated and trained to assess for the presence of mental illness, but not well trained for religious or spiritual assessment. This may be changing, as the Accreditation Council for Graduate Medical Education has created requirements for instruction on religious and spiritual beliefs for psychiatric residents [23]. Earlier editions of American Psychiatric Association's Diagnostic and Statistical Manual (DSM) associated religiosity with severe psychopathology. The DSM-IV added a new diagnostic category for religious and spiritual problems,

thus acknowledging that religious/spiritual beliefs are not inherently pathological, but could be a focus for psychiatric consultation and treatment [78, 79]. Turner and colleagues [79] state that this category contributes to the greater cultural sensitivity incorporated into the DSM-IV and may promote growth of the relationship between psychiatry and the fields of religion and spirituality.

However, the current DSM does not provide criteria for distinguishing between normal and abnormal religious experience, thus clinicians must rely on their clinical judgment and understanding of the local culture [77]. Reliance on culture for determining abnormal religious experience is difficult in a multicultural society. Ng [77] recommends that clinicians acknowledge their own limitations in theological knowledge, and to collaborate or consult with clergy or pastoral mental health professionals when necessary. A study by O'Connor and Vandenberg [80] found that there were discrepancies between clinicians' judgments and the recommendations of the DSM-IV regarding the pathological significance of religious beliefs. Useful criteria for distinguishing religiously-themed psychosis from culturally appropriate religiosity are based on the work of Pierre [81], Lukoff et al. [82], and Sims [83]. The religious or spiritual person without severe mental illness usually recognizes the unusual or extraordinary nature of their ideas or experiences (insight), shares their ideas or experiences with others (inter-subjective reality), has no disturbances in thought processes (conceptual disorganization, looseness of associations, thought blocking), is able to carry out ordinary daily tasks (maintain a job, stay out of legal problems), is not dangerous to others or self (low risk), and usually has a positive outcome over time. It is also important for the clinician to be cognizant that there may be a mix of religious delusions and healthy religious beliefs among individuals living with severe mental illness.

Siddle et al. [76] developed an algorithm for distinguishing religious delusions from normal religious ideas and behavior (p. 132). The algorithm is outlined below.

> Does the patient have a belief (include the attribution of hallucination) which has the characteristics of a delusional idea, for example, an idea which is firmly held; it may be bizarre, and is not amenable to reason? Absolute certainty is not necessary, though there should be more than a suggestion.
>
> Does the patient appear to have any other symptoms of a psychotic illness, for example other delusions, hallucinations, thought disorder, anxiety etc.? This should exclude those who have had an intense religious experience.
>
> Is there a religious content to these ideas expressed? Include such topics as God, the Devil, spirits, angels, etc.
>
> Are any religious ideas expressed likely to be unacceptable to the patient's peers? Would nonpsychotic churchgoing religious people also find these ideas unacceptable?
>
> Are the patient's lifestyle/goals etc. more suggestive of a psychotic episode than an enriching life event?

This algorithm was found to have a good level of agreement (Kappa = 0.75) between the author and a psychiatrist and (Kappa = 0.65) among 12 mental health professionals [76].

Religious delusions can be further categorized based on the content or themes of the delusions [84]. These categories include persecutory (often by the demons), grandiose (believing oneself to be God or an angel), belittlement (to have committed an unforgivable sin), and being controlled (possession). Using the algorithm outlined above in a schizophrenic sample ($n = 193$), Siddle et al. [76] found the prevalence of religious delusions was 24 percent. The most common type of religious delusion was a secondary religious delusion, in which the patient experienced a hallucination that he or she attributed to supernatural beings.

Impact of Religious Delusions on Course of Psychotic Disorder

There is some discrepancy in the literature about whether prognosis is poorer for schizophrenic patients with religious delusions. In Siddle's [76] study, subjects with religious delusions identified themselves as more religious, had more severe symptoms, poorer functioning, longer duration of illness, and were on higher doses of antipsychotic medication. Thara and Eaton [85] followed a sample of individuals ($n = 90$) with first-episode of schizophrenia in India over 10 years; predictive factors for poorer clinical outcome at year ten were religious, sexual and grandiose delusions and flat affect on admission. Males also reported a poorer clinical outcome and spent longer in a psychotic state. Doering et al. [86] found that a strong religious faith was connected with a worse outcome among German patients with schizophrenia ($n = 354$) who were followed over two years. Siddle et al. [87] found (among a sample of 155 schizophrenic or delusional patients) that although patients with religious delusions had baseline and post psychiatric treatment scores that revealed they were more ill compared to patients with other types of delusions, there was no difference in response to treatment (at end of 4 weeks). Patients who self-identified as religious, independent of delusional content, did not differ from peers in baseline features or response to treatment.

Treatment for Patients with Religious Delusions

Mohr et al. [70] reported that in a sample of 236 Swiss and Canadian outpatients with schizophrenia, those reporting religious delusions did not display more severe pathology than others; however, they were found to be less adherent to psychiatric care, to receive less support from religious communities, and to report more negative and less positive religious coping. Among those with religious delusions, more than half (55%) reported that religion was a source of suffering rather than a means of coping.

Because of the unclear relationship of religious delusional content to severity of illness, it has been recommended that clinicians assess pathology of beliefs based on related distress and functional impairment, rather than on the nature of the content [81]. Once impaired functioning is established, standard treatment may be applied.

Cultural and Religious Context of Psychotic Illness

This section will briefly review how religious traditions have viewed psychotic illness in the past, as well as how psychiatry may view religious experiences, and the phenomenon of psychotic patients being treated simultaneously by representatives of religious traditions and by allopathic clinicians.

Most major religions throughout history, and some currently, have viewed psychosis in terms of possession by spirits or demons [88]. Interestingly there is little mention of psychosis in historical texts [24], which may provide some support for the theory that psychosis was rare in ancient times [7]. The nineteenth century experienced a dramatic increase in incidence of severe mental illness. Proposed contributing factors include the increasingly complex industrial society [7] and the spread of infection with rising intercontinental migration [24].

Freud's view that most culturally normative religious beliefs are delusions bordering on psychotic states has led to some of the tension between psychiatry and religion [59]. However Huguelet and Mohr [24] propose that in psychiatry's current biopsychosocial, religion and spirituality complement the other psychological, social and biological domains.

In a Moroccan study [89] the validity of a standardized instrument evaluating psychotic disorders (the Comprehensive Assessment of Symptoms and History or CASH) and an adapted culturally sensitive version (CASH-CS) were tested by comparing them to clinical diagnoses made by local psychiatrists. While the standard instrument showed low agreement with clinical diagnoses, the culturally adapted version displayed good agreement to diagnoses made by local clinicians. The researchers assert that using a standard instrument for assessment of psychosis may lead to cultural misinterpretations, and may explain the high rate of schizophrenia diagnosed in some immigrant groups in Europe. Many experiences considered pathologic to Westerners may be culturally normative. Some Muslims on pilgrimage to Mecca have religious experiences that may be mistaken for delusions. For some Moroccans, hearing sounds or noises inside the mind is considered an expression of their thoughts, not necessarily a hallucinatory experience. Dissociative experiences are relatively common in the Moroccan culture as well as in other parts of Africa, Middle East and Asia. Experiences may include seeing figures or hearing sounds from people or animals; some may enter a trance, often as part of ritual possession during religious ceremonies. Zandi et al. [89] state that generally if any of these experiences are short lived and not limiting role functions, they are usually attributed to religious or cultural phenomenon rather than to a medical condition or psychosis.

Koenig [59] notes that members of religious communities today seldom have difficulty distinguishing culturally appropriate religious beliefs and practices from psychotic symptoms. Milstein and colleagues [90] found that a random national sample of rabbis ($n = 111$) and clinical psychiatrists ($n = 90$) were able to concur in their distinctions among three types of presenting problems: schizophrenic symptomatology, mystical experiences, and mourning. Both groups indicated a

willingness to seek co-professional consultation when encountering such presenting problems.

Seeking treatment for psychosis from indigenous healers is common in more traditional societies, especially when the conceptualization of the illness is rooted in a cultural or spiritual model. However concerns have been raised with some indigenous practices. Indigenous healers may not have the skills to manage psychotic patients, particularly those exhibiting aggressive symptoms. Descriptions have come to light of herbalists tying down violent patients, as well as reports from families of physical and sexual abuse of patients by indigenous healers [91].

In more traditional societies treatment of severe mental illness by indigenous or religious healers may be more prevalent than treatment with allopathic clinicians, even when the latter are easily accessible. It may also be common for individuals with mental illness to receive concurrent treatment from traditional healers and from allopathic clinicians [91, 92]. A Ugandan study [92] investigated explanatory models of 'madness' among indigenous healers ($n = 10$), religious healers ($n = 10$) and allopathic clinicians ($n = 6$). Indigenous healers primarily understood 'madness' as spiritual, for example a curse by a jealous party or a sign the family had deviated from cultural norms; religious healers viewed 'madness' as an influence of an evil spirit or demon, and allopathic clinicians considered the syndrome to be a biological disorder. The clinicians reported an understanding of the patients' worldview of their psychiatric illnesses including causes such as witchcraft, spiritual and ancestral worlds, Satan or God. The clinicians were also aware of parallel management of patients seeking help from indigenous and/or religious healers while also receiving clinical psychiatric treatment. The clinicians reported that they felt that less severe mental disorders such as 'neuroses', could be treated by alternative treatments such as rituals or herbal medicines, but that psychosis needed to be treated primarily with medications.

More extensive family involvement in psychiatric care is common in more traditional cultures as compared to more wealthy societies. For example, a traditional healer in South Africa may require the entire family to be present during rituals in order to be able to communicate with family ancestors to help in reducing symptoms in the ill family member [92].

In this section we focused on the important role of culture and religion/spirituality in determining how psychotic illness is understood. These perspectives on schizophrenia may or may not raise barriers to psychiatric care. In many parts of the world, religious and traditional healing is often sought in parallel with allopathic psychiatric care.

Past and Current Research on Religion in Severe Mental Illness

For many, religious/spiritual coping provides a sense of meaning and purpose, emotional comfort, personal control, intimacy with others and a higher power,

and life transformation [38]. It may be an important mechanism of psychological adjustment, particularly among marginalized groups [93].

Religious Coping

Religious and spiritual coping styles can be either positive or negative, according to the model of Pargament and colleagues [37]. Positive religious and spiritual coping methods, such as turning to religious traditions for strength or to reframe a difficult situation, reflect the perception of a belief in a benevolent higher power and a sense of connectedness with a religious community. Religious and spiritual coping methods classified as negative, such as attributing life's problems to a condemning and abandoning God, reflect belief in a hostile higher power and sense of detachment from a religious community [37].

Given the extreme multiple stressors an individual with severe mental illness must confront, religion and spirituality may be at times the only remaining solace and hope. Relatively few studies have examined relationships between religion and spirituality and psychotic symptoms. In an earlier review of the literature, Koenig et al. [30] identified 16 studies. Among the ten cross-sectional studies, four found less psychosis or psychotic tendencies among people more religiously involved, three found no association, and two studies reported mixed results.

Most studies report a high prevalence of religious and spiritual coping among individuals with severe mental illness. For example a Los Angeles study by Tepper and colleagues [94] found that more than 80 percent of inpatients ($n = 406$) with persistent mental illness reported using religion very frequently to cope. In addition, individuals with schizophrenia spectrum disorders often endorse use of religious coping more often than those with other types of severe mental illness. Reger and Rogers [95] found that among a sample of patients with severe mental illness ($n = 356$), patients with chronic schizophrenia or schizoaffective disorder were more likely to report that religion helped them to cope, compared to those with bipolar or depressive disorders. Likewise, Murray-Swank et al. [96] found that among outpatients ($n = 201$) with serious mental illness, those with schizophrenia or schizoaffective disorder attended religious services and had contact with religious leaders more often than those with a major mood disorder. Severity of psychiatric symptoms was also marginally greater in those having regular contact with a religious leader. Religious behaviors were common in this sample: 53 percent attended religious services, 36 percent had regular contact with a religious leader, and 15 percent received assistance from a religious leader.

The prevalence of religious coping may depend on the patient's particular culture. Wahass and Kent [97] interviewed small samples of Western ($n = 33$) and non-Western ($n = 37$) patients with schizophrenia on how they coped with auditory hallucinations. Investigators found that non-Western patients from Saudi Arabia were more likely than Western patients from Great Britain to use religion to cope (43% versus 3%). Saudi patients prayed, read the Koran, or listened to religious cassettes to help, while British patients depended more on distraction and other

non-religious coping behaviors. However, even in cultures where religious beliefs are less common, religion may still be an important source of coping. Kirov et al. [98] assessed importance of religious faith and religious coping in 52 consecutively admitted psychotic patients in Great Britain. The majority (70%) indicated they were religious and almost one-quarter reported that religion was the most important aspect of their lives. Almost two-thirds of these patients (61%) reported that they used religion to cope with their mental illness, and nearly one-third reported that their religiousness had increased since the onset of their illness. The authors observed that those who indicated they used religion to cope had better insight into their illness and were more compliant with treatment.

Longitudinal studies have found that religious participation may improve the prognosis of patients with psychotic disorders [99, 100]. A study by Verghese et al. [101] followed outpatients ($n = 386$) over two years in India and found that those who reported fewer religious activities at baseline had significantly poorer outcomes. On the other hand, Mohr et al. [102] found that at a three-year follow-up of outpatients with psychotic disorders ($n = 92$) religion was stable over time for almost two-thirds (63%), with 20 percent becoming more religious and 17 percent experiencing losses in their faith. Change in religion did not have an effect on clinical outcome, but was related to lower quality of life and self-esteem.

Yangarber-Hicks [103] examined relationships between religious coping styles and adaptive functioning in persons with severe mental illness living in Ohio ($n = 151$, 47.5% of which were diagnosed with schizophrenia or schizoaffective disorder). Those who coped using a 'collaborative/deferring' approach such as through problem solving in partnership with God and at times deferring to God, reported higher quality of life and more frequent involvement in rehabilitation activities. However a coping style that was self-directed without God's help or one that involved pleading to God for direct intervention was associated with poorer outcomes. Phillips and Stein [104] conducted a qualitative study on young adults diagnosed with schizophrenia ($n = 22$) and bipolar disorder ($n = 26$) recruited from Ohio outpatient clinics. The sample was followed for one year to investigate how their religious coping provided meaning-making in living with severe mental illness. Benevolent religious reappraisals of stressors were associated with positive self-reported mental health, whereas negative religious reappraisals were associated with distress and personal loss. Those with severe mental illness generally used religious meaning-making coping in levels comparable to nonpsychiatric samples. The authors conclude that religious forms of coping may be helpful to make meaning out of the difficult experiences faced by the seriously mentally ill.

Case-studies of three individuals with severe psychotic disorders [105] found that religious beliefs and practices provide a means of destigmatizing the illness and redefining it in religious narratives or spiritual terms. This reframing may make treatment more personally and culturally acceptable to patients. The researchers further suggested that clinicians remain sensitive and value-neutral regarding the uses of religion in a patient's life.

Religious and spiritual coping may also be of importance for caregivers of the severely mentally ill. Rammohan et al. [106] conducted a study among sixty family

members who cared for outpatients with schizophrenia in India. Strength of religious belief along with coping strategies of denial, problem solving and perceived burden were significant predictors of well-being. Based on these findings the authors suggest that the role of religious coping in enhancing well-being of caregivers be considered in family intervention programs.

However, research findings in this area are not always positive. In a qualitative study conducted in Iowa, researchers found that the religious community was not helpful in the coping of individuals with severe mental illness ($n = 17$) [107]. Many participants reported that they felt estranged from and unsupported by their religious communities. However, the majority reported that their personal religious beliefs were important in providing a sense of meaning and hope. Likewise, in a study by Bussema and Bussema [108] among a severely mentally ill sample ($n = 58$), negative psychotic symptoms were exacerbated or not managed well in those endorsing negative religious coping, which included feelings of guilt, despair and judgment by the religious community.

Extensive research has been recently conducted at the University of Geneva on the effects of religion/spirituality on coping, behavior, lifestyle and other health outcomes among patients with schizophrenia. Mohr et al. [109] developed and validated a semi-structured clinical interview for assessment of spiritual and religious coping for use in psychiatric research and clinical work adapted from several different religious and spiritual scales and questionnaires. The assessment covered the religious and spiritual topics of individual history, beliefs, private and public practices, importance in coping with illness, compatibility with treatment, and ease in speaking on the topic with clinicians. Based on a sample of in-person interviews with 100 outpatients, this group found that religion and spirituality are important in coping with the symptoms of schizophrenia and associated life difficulties [110]. Over three-quarters (77%) of subjects reported that spirituality was important or essential in their daily living; over half reported that religion was important or essential in coping with the illness. Private religiosity was more prevalent than group activity: although 78 percent reported a religious affiliation, 56 percent reported never participating in religious services. However, slightly more than half reported participating in individual religious activities each day. The minority of patients that reported psychotic symptoms with religious content described feeling uncomfortable speaking about religion with their clinicians, mainly for fear of being hospitalized.

Huguelet et al. [110] states that although religion and spirituality were reported by the majority of outpatients to be important to their lives and in coping with their illness, their clinicians often underestimated that importance. None of the clinicians reported initiating conversations about religion with their outpatients, although the majority (93%) of the clinicians reported feeling at ease to speak about the topic. Most of the outpatients (87%) felt that there was no incompatibility of religiosity with treatment or supportive psychotherapy, and most felt at ease to talk about religion with their clinician (79%). However, less than half (40%) of the outpatients reported actually talking about religion with their clinician.

Among the same sample, 71 percent reported that religious beliefs instilled hope, purpose, and meaning in their lives, but 14 percent said it induced spiritual despair [111]. Over half reported that it lessened psychotic and other pathological symptoms, while 10 percent reported it increased symptoms. Almost one-third (28%) reported it increased social integration. One-third reported it helped to prevent suicide attempts, while 10 percent felt religious issues contributed to their attempts. Fourteen percent reported that religious involvement reduced substance abuse. Sixteen percent stated that religion helped with their treatment adherence, while 15 percent felt that their religious beliefs were in opposition to treatment. Thus, overall, the authors conclude that religion played more of a positive than a negative role in the lives and treatment of these patients.

Huguelet and Mohr [24] explain that religion and spirituality may increase support and relieve stress through helping to manage symptoms and life difficulties, providing comfort and meaning in suffering and providing social support through peers and clergy. As most individuals living with schizophrenia have very restricted lives marked by disability and isolation, finding hope, fulfillment, personal growth and self-esteem through religion and spirituality may be important in coping. Keks and D'Souza [112] state that spirituality may be critical for dealing with the loss that psychoses effects on identity and personality. Religion and spirituality may replace some of the loss, and may also play a key role in psychotherapeutic support. However religion may also be a source of pain, guilt and exclusion, and religious themes may also play a negative role in psychopathology.

Further studies are needed, especially given that most are cross-sectional. Across-sectional design study limits the ability to determine causality, in other words, whether religion is common among the severely mentally ill because it helps them to cope, or whether preexisting religious traits contribute to the development of the illness. Of special interest with regard to public religious activity is its relationship to paranoia, a common symptom in schizophrenia. Less symptomatic patients may be more comfortable participating in church services, for example, because of lower levels of paranoia. If service attendance and paranoia were measured concurrently, it might appear that attendance relieved paranoia even if this were not the case. However based on the studies conducted thus far, religious and spiritual beliefs and practices appear to help some individuals living with severe mental illness to cope better with the symptoms of the illness and its devastating personal and social consequences.

Adherence to Treatment

Perhaps the most clinically-relevant research in this area explores how religious and spiritual beliefs and practices influence adherence to psychiatric treatment. One of the few studies on the topic was conducted by Borras et al. [113]. The researchers assessed medication adherence during the last one year time period by interviewing outpatients ($n = 103$) and their psychiatrists, and by blood drug monitoring. Eighty-three percent of the outpatients were on oral antipsychotic medication while

the remainder were on depot antipsychotic medication. Among outpatients treated orally, 32 percent were completely or partially nonadherent. Adherent patients reported participating in group religious practices more and were more likely to endorse community support as important to them; these associations became nonsignificant when controlling for other factors such as positive psychotic symptoms and substance use. However, the importance of religion in the lives of the outpatients was also significantly associated with lower levels of substance abuse and more symptomatic remission.

Borras et al. examined the qualitative relationship among the outpatients' view of their illness and their religious and spiritual beliefs and role in treatment adherence. Over half (57%) of the outpatients reported that their religious and spiritual beliefs directly influenced their perception of the illness. Among these, one-third asserted that religion/spirituality gave a positive meaning to their illness, such as the severe mental illness being a part of God's plan or a gift to encourage spiritual growth; while approximately one-quarter endorsed negative religious views of schizophrenia, such as the illness being a punishment from God. The remaining 43 percent described viewing the illness from a medical perspective only. The religious/spiritual view of the illness was more prominent among the nonadherent outpatients. A significant proportion of nonadherent subjects (31% of completely nonadherent and 27% of partially adherent) felt there was an incompatibility between their religious or spiritual beliefs and taking medications; only eight percent of adherent outpatients expressed this feeling. A minority of subjects also reported a contradiction between their religion/spirituality and supportive psychotherapy. Explanations for the conflict included the belief that only God could heal or that the illness is part of a divine plan. The investigators state that psychiatric treatment may be in conflict with certain teachings of various religious groups. Beyond medication therapy, the psychiatrist's behavioral recommendations to take care of oneself, learn to say no, and encourage self-accomplishment may be felt to be in conflict with religious teachings of service to others, self-sacrifice, and the benefits of suffering.

A study by Mitchell and Romans [114], among bipolar patients ($n = 147$) reported similar findings, with over one-third (37%) reporting a religious/spiritual view of the illness and one-third (32%) reporting incompatibility between their beliefs and treatment. Thus, it is imperative that clinicians not underestimate the importance of religious issues for psychotic patients, and understand how psychiatric treatments fit into their overall worldview. In a study by Mohr et al. [70] ($n = 236$), religious delusions were not associated with a more severe clinical status, but patients with religious delusions were less likely to adhere to psychiatric treatment.

Suicide

Prior reviews of the literature have demonstrated an inverse relationship between religion and suicide [55]. Nevertheless, little is known about the effect of spirituality

and religion on suicide risk among patients with schizophrenia [115]. Palmer et al. [116] estimate based on a meta-analysis that 4.9 percent of individuals living with schizophrenia commit suicide, with suicides concentrated early in the course of the illness; thus prevention efforts are recommended from the onset of psychosis. In a qualitative study, psychotic subjects ($n = 8$) identified religious and spiritual beliefs, such as a relationship with a higher power, as one of only a few protective factors against suicide [117].

Jarbin and von Knorring [118] conducted a study among Swedish inpatients with adolescent-onset psychiatric disorders ($n = 88$), half of which were diagnosed with schizophrenia spectrum disorder and were followed-up after 10 years. One-quarter were found to have attempted suicide and 4.5 percent had died from suicide. Protective factors against suicidal behavior were satisfaction with religion, health, family relations and safety. Controlling for concurrent symptoms of anxiety and depression, only satisfaction with religious belief retained significance as a protective factor. However, on subanalysis of those with schizophrenia spectrum disorders, the association between suicide attempts and satisfaction with religious beliefs did not reach statistical significance. There was no correlation between participation in religious activities and suicide attempts in the overall sample.

Huguelet et al. [115] conducted a study to assess the level of religiousness and spirituality among three groups, (1) outpatients with schizophrenia with prior suicide attempts ($n = 50$), (2) outpatients with schizophrenia with no prior suicide attempts ($n = 65$), and (3) nonpsychotic inpatients with at least one suicide attempt ($n = 30$). It was found that patients with psychosis who had attempted suicide had been ill longer and hospitalized more frequently. In regards to religion, almost half (42%) reported that religion occupied a central role in their lives, and most reported a religious affiliation (83%). Almost two-thirds (64%) of participants reported no relationship between religion and suicide attempts, while one-quarter reported a protective role, and 11 percent reported religion as a risk factor. Subjects described using religious coping to fight despair and suicidal thoughts; they additionally noted that religious condemnation of suicide was protective. On the other hand, some subjects related suicidal behavior to religious themes, for example the stress of leaving a religious community or losing faith, religious delusions and hallucinations, anger with God, and the wish to die to be with God. Given these mixed results, and the high rate of suicidal behavior among individuals living with schizophrenia, further research on this topic is needed.

Substance Use/Abuse

The protective influence of religion and spirituality against substance abuse is well documented [30, 39]. Substance abuse is a prevalent problem among individuals living with schizophrenia and of vital importance in improving outcomes; yet it is unclear how the protective effect of religion and spirituality may relate to substance abuse among those with schizophrenia. The National Institute of Mental Health Epidemiologic Catchment Area (ECA) study ($n = 20{,}291$), found that 47 percent of

those with schizophrenia or schizophreniform disorder also had a history of some form of substance abuse-dependence [119]. The odds of having a substance abuse diagnosis were 4.6 times as high for those with schizophrenia as for the general population studied; individuals living with schizophrenia were three times as likely as others to have an alcohol abuse/dependence diagnosis, and six times as likely to use illicit drugs. The majority of those with schizophrenia in prison populations were reported to have a co-morbidity of substance abuse disorder (85.8% for alcohol disorder and 72.4% for any other drug disorder).

Huguelet et al. [120] found that among outpatients with schizophrenia ($n = 115$), religiousness and spirituality were inversely related to substance use and abuse. Religion was found to be protective against substance abuse in over 10 percent of the overall sample and among almost half (42%) of individuals in recovery from substance abuse. Only three percent reported that religion played a deleterious role in their substance use. The protective role of religion against substance abuse as reported by the study participants included providing guidelines for living without toxic substances, an alternative coping strategy to replace substance abuse, and assistance for reorganizing life around spirituality. The negative role of religion in substance abuse as reported by study participants was rejection or loss of a religious community and subsequent use of drugs to cope with the distress of the rejection.

Subjects who considered religion unimportant were more likely to be current substance abusers than those who deemed religion important (47% vs. 29% respectively). The lowest rate of current substance abuse, 9 percent, was found among subjects who rated religion as important and also affiliated with a religious community. Those who reported receiving a religious education in childhood were significantly less likely to have ever been substance abusers.

Cigarette Smoking

The protective role of religiousness and spirituality against smoking is well-known in the general population, but has been rarely studied among individuals living with schizophrenia [121]. Smoking is more prevalent among individuals living with schizophrenia than in the general population. A study by McCreadie [122] found that 65 percent of individuals with schizophrenia ($n = 316$) were current smokers compared to 40 percent of the general population matched controls ($n = 250$). Those with schizophrenia were also more likely to be heavy smokers (20 or more cigarettes per day) compared to the general population (76% vs. 46%); and die earlier especially from smoking-related diseases [123]. Possible biological explanations for the increased prevalence are that the nicotine may relieve positive and negative symptoms and lessen adverse effects of antipsychotic medications [124, 125].

A Swiss study [121] found that the rates of cigarette smoking among patients with schizophrenia ($n = 115$) were two to four times community rates. Over half (58%) were current smokers, and 27 percent were heavy smokers. Religiosity was negatively associated with tobacco use. There were significantly more current smokers without religious affiliation than non-smokers. Non-smokers reported

significantly more frequent group religious practices and rated support of the religious community as more important than did smokers, even after controlling for demographic confounders [121]. The authors recommended that based on these findings it may be helpful for clinicians to learn about the spiritual lives of their patients and to reinforce these resources when appropriate. However further systematic exploration of religious issues in the care of individuals living with schizophrenia and who also smoke is needed.

Quality of Life (QOL)

Religion has been found to be important to quality of life (QOL) among outpatients living with schizophrenia. A multi-site European study assessed multiple domains of QOL using a multidimensional measure; among schizophrenic respondents ($n = 404$), the domain of religious QOL was rated more highly than all other domains [126]. Mohr and colleagues [109], however, found no correlation between subjective QOL (measured by self-reported level of happiness) and religiosity among outpatients with schizophrenia ($n = 115$). As schizophrenia is a chronic illness with no known cure, quality of life is an important outcome measure. A study by Nolan and colleagues (under review) [127] investigated the relationship between religious coping and quality of life using the multidimensional quality of life instrument of the World Health Organization Quality of Life-BREF (WHOQOL-BREF) among a sample of 63 outpatients with schizophrenia or schizo-affective disorder. The majority of the sample reported religious and spiritual coping as important to essential. Positive religious coping significantly correlated with the QOL domain of psychological health, with a positive trend for the domain of physical health. Negative religious coping and overall quality of life were inversely related. Further study is needed to validate these initial findings.

Comorbidity with HIV/AIDS

Previous research has found that spirituality may buffer stress among those living with HIV/AIDS [128, 129]. A study of urban, socially disenfranchised women living with HIV/AIDS ($n = 230$) found spiritual coping to be of benefit, even after controlling for other types of coping [130]. Individuals living with schizophrenia are especially vulnerable to contracting HIV/AIDS. In a sample of patients with severe mental illness ($n = 931$), two-thirds of which had a diagnosis of schizophrenia or schizoaffective disorder, the prevalence of HIV/AIDS was almost ten times higher than the general population (3.1% versus 0.32%) [131, 132]. A metaanalysis by Cournos and McKinnon [133] found the seroprevalence of HIV among Americans with schizophrenia to be 9.2 percent. The rate was particularly high among those with dual diagnosis of severe mental illness and substance use disorder (18.4%).

In a qualitative study by Loue and Sajatovic [134] among severely mentally ill women ($n = 41$), a large proportion reported that their religious and spiritual beliefs were critical to their coping, had influenced them to reduce risk to HIV, and/or provided them with needed social support. Several participants also reported having experienced rejection from their faith communities. Further study of these issues is indicated.

In summary, religious and spiritual beliefs and practices are common for coping, and appear to have some relationship to lifestyle behaviors and health outcomes among individuals living with schizophrenia. Given the potential for interaction of beliefs, risk behaviors, and outcomes, clinicians should attempt to understand the role that religion and spirituality play in the lives of their patients. Further longitudinal studies should elucidate these complex issues and better inform treatment.

Directions for Future Research

Although there have been some initial studies on religion and spirituality among those with schizophrenia, there are few validated instruments for this population. Religious/spiritual measures that are validated among individuals living with schizophrenia will be important to confirm and advance current research. Such an instrument is also needed for clinical use, to help mental health providers better know and understand the role of religiosity or spirituality in the lives of their patients.

One existing spiritual assessment was recently developed by Mohr and colleagues at the University of Geneva for research and clinical use [109]. This semi-structured interview provides a comprehensive survey of the place of religion and spirituality in the individual's life, including queries regarding beliefs, private and public practices, religious and spiritual coping, and compatibility of religious beliefs with mental health treatment. The instrument is administered with the aid of a visual analog scale, and adaptation of language to the individual beliefs and practices of the client. It has been found to have high construct validity and inter-rater reliability; administration requires no specific training. It has also been shown to have applicability in a diversity of religious beliefs including those that may be considered pathological. It is currently being tested in community samples in North America, Africa and Europe for its applicability, validity, and reliability.

Another need in studying religiosity among individuals living with schizophrenia is valid and reliable methods for distinguishing religious delusions from culturally normative religious beliefs. While some guidelines have been suggested by various authors [76, 81–83, 135], these are in need of reliability testing, as well as validation in a range of cultural settings and faith traditions.

Koenig [59] (pp. 44–45) has suggested some possible future research questions on the presentation of symptoms, such as religious delusions or hallucinations, and how they vary depending on the faith tradition and culture, in order to distinguish such symptoms from culturally normative beliefs and behaviors.

- How do people with schizophrenia and other psychotic disorders from different religious traditions present in terms of symptoms or experiences with religious content?
- What distinct features separate these persons demonstrating psychopathology from healthy persons in their religious tradition?
- In persons with schizophrenia and other psychotic disorders, how can one distinguish religious beliefs, practices and experiences that have a positive impact on coping and disease course from those that negatively impact prognosis (and are part of their psychopathology)?
- How is the expression of religiousness different in persons actively symptomatic with psychotic disorders from those with psychotic disorders whose symptoms are controlled?
- What effect does treatment with anti psychotic medication have on religious beliefs, behaviors and experiences (both 'normal' and pathological ones) in persons with schizophrenia and other psychotic disorders?
- What is the relationship (if any) between religious conversion experiences and the onset of psychotic disorders? What kinds of religious conversions are linked with the precipitation of psychosis? (i.e., those that are slow and gradual vs. sudden; conversion to one religious tradition vs. another; etc.)? Does a predisposition to schizophrenia and other psychotic disorders make one more likely to experience certain types of religious conversion?
- What effects do age, gender, ethnicity, and education/socioeconomic status have on the answers to these questions?
- What effects does the presence of various medical and neurological conditions have on the answers to these questions (including HIV/AIDS with and without nervous system involvement)?
- Are there specific biological and/or psychodynamic causes for religious delusions or hallucinations? (Or are these entirely culturally determined?)

Huguelet and Mohr [24] have conducted the most comprehensive studies on the relationship between religious and spiritual beliefs and practices and outcomes related to schizophrenia. However their studies have been mainly cross-sectional. The lack of research in this area is a major barrier to diagnostic assessment and future clinical applications. Koenig [59] states that there are almost no research questions in this area that have been adequately studied, thus the possibilities for future studies are almost limitless and present both a unique and challenging opportunity for researchers.

Future research should focus on possible effects of religion and spirituality on the long-term course of schizophrenia, attempting to distinguish normative spiritual beliefs and practices from religious delusions. Such research could conceivably observe patients from the prodromal phase into the later stages of illness; cross-cultural study will no doubt help distinguish environmental from primarily biological phenomena. More research is also needed regarding how culture affects referral to and compliance with treatment.

Koenig [59] (p. 46) has presented some possible future research questions on how pathological and nonpathological religious beliefs, practices and experiences may impact on course of illness and other outcomes. Outcome measures may include behaviors such as adherence to treatment, substance use/abuse, suicidality, as well as quality of life, self-esteem, etc.

- Do persons with religious delusions or hallucinations have a worse prognosis or response to treatment? How is compliance affected?
- Are there specific types of religious delusions or hallucinations that portend a particularly poor prognosis?
- What impact do 'healthy' religious beliefs, practices and experiences have on disease course/outcome for persons with schizophrenia and other psychotic disorders? Are there certain practices that are healthier than others (i.e., involvement in religious community vs. private religious activities)? Are certain religious practices synergistic with biological treatments in terms of efficacy?
- Is the impact of religious delusions or healthy religious beliefs on disease course stronger for certain psychotic disorders more than for others (e.g., schizophrenia vs. bipolar mania vs. delusional disorder, etc.)?
- How does religious involvement affect the risk and course of comorbid substance abuse in persons with schizophrenia and other psychotic disorders? How does it affect the course of illness in this population?
- Can sensitive and sensible spiritual interventions be developed (specific for each religious tradition) and tested for efficacy (improvement) and side effects (worsening psychosis)?
- Does removal of any religious influences or symbols during the acute treatment phase facilitate or hinder recovery of the religious patients with schizophrenia and other psychotic disorders?

Misunderstanding and stigma in community religious organizations may create barriers to social integration for many of the severely mentally ill. Thus there is a need for development and studies on the effectiveness of mental health education programs for religious leaders and their congregations. Another avenue to explore is development of collaborative programs in which mental health and faith-based organizations collaborate in enhancing support among congregants living with schizophrenia. In addition, more information is needed on traditional treatments being applied in less wealthy countries, and how they may relate to the medical model. Another area that needs to be investigated further is what barriers inhibit clinicians from discussing religious/spiritual issues with patients.

In summary, research in the area of religiosity/spirituality and schizophrenia is in its infancy. Advancements in measurement as well as in-depth prospective research will likely yield findings with potential to improve multiple mental health and quality of life outcomes for those with major psychoses.

Implications for Treatment and Community Interventions

Religion and spirituality may help some individuals living with schizophrenia through coping with symptoms and stressors, as well as preventing harmful behaviors such as substance abuse and suicide attempts. However, there is also reason to believe that religion and spirituality may precipitate or exacerbate symptoms in some vulnerable individuals. Some religious belief systems may also encourage noncompliance with medical treatment.

There are no guidelines in the scientific literature on incorporation of religious or spiritual issues in the individual care of patients with psychosis. However, some researchers, such as Fallot [71] recommend conducting a spiritual assessment, addressing spiritual and religious needs in individual psychotherapy once the illness is stabilized, connecting the patient to faith communities and spiritual resources, or, more controversially, conducting group therapy with a spiritual or religious component. In the following paragraphs are some general suggestions based on existing research that may be of assistance to clinicians.

Given the prevalence of religious and spiritual coping that has been observed in those with schizophrenia and in other populations with mental health problems, a spiritual assessment is recommended as part of the psychiatric evaluation [136]. In making this assessment, the interviewer should bear in mind that religion and spirituality may function for each individual patient in different, or multiple, ways. Religious delusions may exist transiently in the context of lifelong religious devotion. Mainstream spiritual beliefs and practices may lead the patient to reject psychiatric treatment. A religious community may provide a supportive network, or may reject those who seem different. Religious coping methods may be adaptive in some situations and not in others. Therefore, spiritual assessment is not so much an addition to the clinical interview, but rather a key component of getting to know the patient well and to understand his/her particular strengths and challenges.

In administering the assessment the centrality or importance of religion and spirituality in the patient needs to be assessed by asking questions about religious background, current beliefs and practices, and the overall importance of religiosity in the patient's life [109]. Based on responses to these questions, the clinician can estimate centrality. For patients with low centrality, such as for those with no or few practices and for whom religion has never been important, further questions on coping and compatibility with treatment are omitted, and the clinician can explore what other resources the patient has available for coping and support. If centrality is medium to high, further discussion of spiritual coping and compatibility of religious beliefs with treatment may be appropriate.

Likewise, the clinician needs to distinguish between culturally normative religious beliefs and experiences from religious delusions and hallucinations. Delusional religious ideas may run on a continuum with normal religious beliefs [76]. If a religious delusion is established, Mohr and Pfeifer [135] recommend that the delusional condition be given standard treatment for such symptoms, including

medication, psychotherapy and social support from family, and if applicable support from religious communities.

Lukoff [137] comments that although spirituality has been part of the therapeutic treatment for substance abuse, as in 12-step programs, it is new for treatment of serious mental disorders. This is part of a 'recovery model', recommended for the mental health system by the Surgeon General in a 1999 report [138]. The recovery model does not imply a cure nor ignore the chronic nature of the disorder. It simply attempts to reframe the illness from negative terms (as in symptoms to be eliminated) used in the medical model, into more positive goals: improving quality of life, using and enhancing client strengths, and achieving functional improvements. Rehabilitation programs utilizing the recovery model may encourage healthcare professionals to act as 'coaches' when appropriate to motivate and focus clients to help themselves; this may include respecting and supporting the spiritual journey of the client.

Fallot [139] recommends that providers communicate to patients that they are interested in and responsive to the spiritual dimension of their lives, and that they will consider incorporating this factor in service planning if the patient wishes. Fallot also recommends that some programs consider inclusion of the spiritual dimension to structured individual or group interventions, exploring how spirituality may function positively and/or negatively for patients.

Treatment should promote human flourishing and development, despite chronic illness [71]. Religious or spiritual involvement may assist patients in establishing their own identity, a normal developmental task often disrupted by such a devastating mental illness as schizophrenia. Religion and spirituality may offer an identity of being a 'whole person', a unique individual, rather than just an individual with a psychiatric diagnosis.

Although individuals living with schizophrenia may report high frequency of private religious practices such as prayer, meditation and spiritual reading, public religious behavior is somewhat more rare. This likely relates to interpersonal discomfort, given the difficulties in development of interpersonal relationships associated with both positive and negative psychotic symptoms. However if these relationships can be developed it may provide an important social support system for the severely mentally ill patient [24].

Treatment Interventions

A qualitative study by Murphy [117] among eight psychotic patients found that an integrated approach to treatment, incorporating standard treatments as well as addressing the spiritual life of the patient, was beneficial. Given the catastrophic effects of schizophrenia for a young person just emerging from adolescence, many patients experience an existential crisis and begin to wonder if life is worthwhile. However many reported that religious faith or personal spiritual conviction provided them with answers to questions about meaning and purpose in life. The investigator

concluded that when providers listen to spiritual beliefs held by patients, it aids in the healing process.

A few authors have described integration of spiritual themes into group therapy for patients with major psychoses. Phillips et al. [140] implemented a seven week semi-structured psychoeducational intervention in which outpatients with severe mental illness ($n = 10$) discussed religious resources, spiritual struggles, forgiveness and hope. The majority (70%) indicated that they attended church weekly; all indicated that they attended church at least several times a year and prayed at least monthly. The group met once a week for 1.5 hours over the course of seven weeks with a psychoeductional format. The intervention provided a safe environment to discuss both uplifting and distressing aspects of participants' spirituality. Participants described this as a valued experience, and did not report feeling any element of proselytization or coercion. The group did not appear to trigger any serious emotional disturbances.

Kehoe [141, 142] describes her experiences of over 20 years of conducting therapy groups among the seriously mentally ill that focus on spiritual beliefs and values. Kehoe stresses that it is a discussion group, rather than a prayer or study group. The groups foster tolerance, self-awareness, and nonpathogenic therapeutic exploration of value systems. Group rules include tolerance of diversity, respect of others' beliefs, open enrollment and a ban on proselytizing. The author describes the group as a nonjudgmental environment for participants to explore their spirituality; she feels spirituality often provides clients with a sense of identity beyond their mental illness. Kehoe states that concerns that the therapy would promote religious delusions or be counterproductive to treatment have not been borne out in any patient over the 20 years she has led the groups.

A structured group treatment, described by Revheim and Greenberg [143] addresses spirituality for outpatients and inpatients with schizophrenia; groups are conducted by both clinicians and religious leaders. Activities are designed to facilitate verbal expression, appropriate social interaction, and build a sense of community. Revheim and Greenberg [143] note that the highly structured group format accommodates cognitive deficits and limited social skills, which are prevalent in persons with persistent psychiatric disabilities.

Psychosocial interventions with a spirituality component may positively influence the course of severe mental illness, by providing a safe and supportive environment to discuss spiritual concerns and promote social connections with others. However none of these individual or group oriented interventions have yet been tested for efficacy and safety in randomized clinical trials.

Community Interventions

As described earlier in this chapter, community resources for those with schizophrenia are currently inadequate. Public sector efforts to correct this deficiency will likely be slow and stymied by pressure from more powerful political factions. In the face of this crisis, alternative treatment models must be considered. Religious

organizations exist in all parts of the globe, often with complex and stable infrastructure committed to reducing human suffering. Collaboration of faith communities with mental health advocates and providers could result in great improvements in community support available to the severely mentally ill.

For the past several decades, health care and religious organizations have existed in parallel, with little collaboration or communication. Although mental health practitioners and religious leaders may aim to help the same groups of people, they may be offering to these groups contrasting and possibly incompatible models of the same pathology. To bridge this gap to the advantage of the mentally ill, health care providers and religious leaders must enter a mutually respectful dialogue.

Clinicians need to be informed and aware of faith based organizations in the community which may be open and supportive to the needs of their clients. Some faith-based groups may be rejecting of individuals with schizophrenia due to behavior or appearance. Outreach to religious groups must include psychoeducation aimed at the acceptance and support of the severely mentally ill. In addition, health care practitioners must be willing to work with such organizations in a way that is respectful of an alternate worldview, as opposed to a one-sided educational crusade promoting the medical model.

Such collaborative models may be of greatest importance in less wealthy countries, where mental health treatment is largely unavailable. Given the role of local religious traditions in the understanding of the cause and treatment of mental illness, religious organizations may provide a means of providing mental health care, through provision of training in psychoeducation and counseling among religious leaders. In areas of the world with limited or no access to treatment, this approach may offer a relatively low cost alternative to mental health services.

For example in Tanzania, mental health services are almost nonexistent in most areas of the country, with less than a dozen psychiatrists and even fewer psychologists in the entire country of a population of 35 million. Johnson and colleagues [144] described a pilot program implemented in the Kilimanjaro region that partnered mental health researchers with local religious institutions. This program trained local hospital chaplains, social workers and nurses to lead a small group of outpatients and their family members in psychoeducation classes; this project aimed to promote understanding and management of symptoms, and to improve quality of life and integration in the community, while respecting local cultural beliefs and practices.

Traditional community resources such as temple healing practices are widely used in managing mental illness in India [145]. Many people with serious mental illness go to religious centers of Hindu, Muslim or Christian faith. Raguram and colleagues [145] conducted a study on clinical effectiveness of religious healing at a Hindu healing temple in South India. The temple is known in the area as a refuge for people with serious mental disorders. The authors conducted semi-structured interviews of patients ($n = 31$; 23 of whom were diagnosed with paranoid schizophrenia) and caregivers on their views of the illness and its cause. The impact of the stay in the temple was measured by severity of psychopathology assessed by the brief

psychiatric rating scale by a trained psychiatrist at baseline and follow-up. The average length of stay was six weeks; only one subject had had previous medical care for the condition, and none had been treated by a psychiatrist.

Patients showed statistically and clinically significant improvement during their stays. Twenty-two subjects improved and three recovered fully. The investigators state that no rituals were performed, only simple morning prayers; the rest of the day spent in light maintenance routines around the temple. The healing effects may have been from the supportive, non-threatening environment and from the cultural belief in the healing power of the temple. Although local government-run primary health centers are designated as care providers for the mentally ill in such rural areas, traditional religious resources are much more frequently used. The findings of this study, although not generalizable, highlight the importance of considering indigenous local resources to aid in planning for mental health services and treatment, particularly in areas with limited access to psychiatric care.

However, spiritual, religious and traditional treatments for severe mental illness do not always result in improvement. A case-control study of Egyptian patients with schizophrenia ($n = 40$) compared those with and without previous exposure to traditional spiritual healing practices. Cases who reported a spiritual healing relapsed significantly more frequently than controls over a period of 18 months. Relapse was four times more likely among patients receiving exorcism or witchcraft; there was no relationship between greater intensity of personal religious beliefs/practices and risk of relapse [146].

Summary and Conclusions

Schizophrenia is a devastating chronic illness, associated with social, economic and emotional difficulties. Most treatments manage the symptoms, through the biopsychosocial model, including antipsychotic medications, psychological interventions, and family and social support. Most often, the religious/spiritual lives of patients living with schizophrenia are not addressed in treatment. Research has shown that many patients with schizophrenia hold very strong religious beliefs, engage in private as well as group religious activities, and rely on spiritual resources to cope with the overwhelming stress of chronic psychosis. These belief systems may affect health behaviors, mental health outcomes, and adherence with treatment. Therefore, understanding of this aspect of patients' lives, regardless of diagnosis, is vital to providing quality mental health care.

A spiritual assessment can assist the practitioner in determining the relevance of religious and spiritual beliefs and practices to the individual patient. Individual and group therapies that integrate religious and spiritual components, although not yet subjected to rigorous testing for efficacy and safety, are being developed and implemented. Such therapies may be of benefit for addressing spiritual concerns and enhancing social integration. Collaborative initiatives linking mental health care providers with local religious bodies may help to connect individuals living with

schizophrenia with needed community resources, and ultimately may ameliorate the critical shortage of available treatment for the severely mentally ill.

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Chapter 18
The Ethical Ramifications of Biomarker Use for Mood Disorders

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Abstract Over the past 20 years, researchers have made considerable progress in the search for diagnostic and prognostic biomarkers of psychiatric disorders, including major depressive disorder, bipolar disorder, and anxiety. Advocates of this research contend that identifying biomarkers will aid in the diagnosis and treatment of these disorders, as well as in the development of more effective psychiatric medications. However, the concept of biomarker testing generates significant ethical concerns, including the testing of non-symptomatic individuals, the potential for health insurance or employment discrimination, and the collection and use of genetic information. Genetic biomarkers are especially controversial since heredity information is uniquely personal – it can reveal an individual's likely medical future; divulge personal information about one's parents, siblings and children; and has a history of being used to stigmatize and victimize individuals. Some legal protections are already in place; however, they are far from comprehensive. For example, the US Genetic Information Nondiscrimination Act of 2008 only encompasses tests that analyze DNA, RNA, or chromosomal changes. This means that tests for non-genetic biomarkers, like those based on protein expression or post-translational modifications, are exempt. In the rush toward developing etiological screening tools, it is pertinent to remember that patients are at the heart of the medical profession, not their DNA or protein profile. Any new diagnostic tools should confer a significant benefit to patients without promoting confusion, discrimination, or stigma.

Keywords Ethics · Biomarker · Psychiatric disorders · Depression · Anxiety · Genetic · Protein · Epigenetic · Diagnosis · Pharmacogenomics

Abbreviations

5HTT	5-hydroxytryptamine
ABCB1	ATB-binding cassette subfamily B member 1
ACTH	Adrenocorticotropic hormone

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BDNF	Brain derived neurotrophic factor
BRCA	Breast cancer gene
CRF	Corticotropin releasing factor
DNA	Deoxyribonucleic acid
DNMT	DNA methyltransferase
DSM-IV	Diagnostic and statistical manual of mental disorders
GABA	γ-aminobutyric acid receptor
GAD-7	Generalized anxiety disorder-7
GINA	Genetic Information Non-discrimination Act
GR	Glucocorticoid receptor
GWA	Genome wide analysis
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary adrenal
MDQ	Mood disorder questionnaire
MDR1	Multidrug resistance 1
MR	Mineralcorticoid receptor
mRNA	Messenger RNA
NEO-PI	NEO personality inventory
NPY	Neuropeptide Y
NR3C1	Nuclear receptor subfamily 3, group C, member 1
PHQ	Patient health questionnaire
PPD	Purified protein derivative
RNA	Ribonucleic acid
SCID	Structured clinical interview for DSM-IV
SNPs	Single nucleotide polymorphisms
SSRIs	Serotonin reuptake inhibitors
TB	Tuberculosis

Introduction

Psychiatric illness affects millions of people around the world. Of these illnesses, depression and anxiety are two of the most common, affecting nearly 55 million people in the United States alone [1]. However, despite the story these statistics may tell, distinguishing between specific psychiatric conditions is an inaccurate process. Over the last decade, a scientific and public push for better diagnostic criteria based on quantifiable methods has resulted in the melding of biomarker research with psychiatry. While this seems like a boon for patients in theory, the practical applications of such biomarker technology in psychiatry has raised some pressing ethical issues, especially since any new test is not likely to be 100% reliable. So what is ultimately best for the patients? Do the benefits of more objective, technology-based diagnoses outweigh the potential confusion, discrimination, or stigma such testing may cause? This is what this chapter hopes to elucidate.

But first, what is a biomarker? A biomarker is any tool that can be used in the diagnosis, prediction, or etiology of a specific illness, syndrome or disease. It can be

a gene, a protein, a metabolite, brain imaging such as functional magnetic resonance imaging, or epigenetic. All of these areas are currently being studied for their uses in identifying biomarkers associated with psychiatric disorders. Unfortunately, identifying a biomarker with absolute predictive value for psychiatric illnesses has proven more difficult than expected, mainly due to the multifactorial etiology of these conditions. The ethical ramifications of success, especially with regards to biomarkers' predictive power, have put further pressure on the field. So much so, that a new subfield within bioethics called neuroethics has emerged to address ethical issues regarding psychiatric disorders among many other neurological issues [2].

How far have researchers come, though? There actually have been a number of recent advances in the development of predictive and diagnostic biomarkers for depression (unipolar and bipolar) and anxiety disorders that have brought testing (and potentially individualized treatments) nearer to reality.

Current Psychiatric Diagnostic Tools

Diagnosing unipolar depression, bipolar disorder, anxiety, and other psychiatric illnesses currently relies solely on patient-based reporting of symptoms on common questionnaires such as the Mood Disorder Questionnaire (MDQ) and Generalized Anxiety Disorder-7 (GAD-7) and the clinician's interpretation of said symptoms based on the guidelines laid out in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the diagnostic standard for mental health professionals in the United States. Therefore, making an accurate diagnosis is often a process of trial and error since it is predicated on the patient's truthfulness in reporting symptoms, as well as subjective interpretation of diagnostic criteria. Statistics show that patients often do not accurately report their symptoms out of fear of being stigmatized, which further complicates diagnosis when coupled with the primary care practitioner's reflective fear [3]. As a result, misdiagnosis and under diagnosis are common occurrences [3–5].

The validity of the questionnaires used to assess a patient's symptoms has also been the subject of intense investigation [6–9]. A recent study investigating the accuracy of the Mood Disorder Questionnaire (MDQ) usually used to diagnose bipolar disorder found that patients with positive results were as likely to be diagnosed with borderline personality disorder as bipolar disorder, calling into question the clinical usefulness of the MDQ in clinical practice [10]. Another study focusing on the Patient Health Questionnaire (PHQ) suggested it may not adequately identify anxiety and depressive disorders [11]. According to the results of this study, half of the study participants had been previously diagnosed with at least one anxiety disorder; however, nearly 50% of these individuals were classified by the PHQ as healthy. The PHQ also missed one third of major depressive disorder cases and only identified one case out of seven for other depressive disorders. Even the validity of the Structure Clinical Interview for DSM-III-R and DSM-IV (SCID), the supposed "gold standard" for psychiatric diagnosis, has shown an enormous range of reliability in clinical testing, depending on the makeup of the sample and the research

methodology. For example, Skodol et al. determined that the diagnostic power of the SCID varied with diagnosis, from 0.45 for narcissistic to 0.95 for antisocial disorder [12].

Because of the unreliability and subjectivity of current diagnostic tools, both the public and scientific communities have pushed for the development of biochemical screenings. While this work is still in its early stages, strides have been made in identifying potential biomarkers for implementation in screening tests that could provide a more definitive basis for the diagnosis of psychiatric disorders.

Potential Biomarkers for Depression

In 1999, Ghaemi et al. reported that 40% of patients with bipolar disorder in their study group had previously been misdiagnosed as having major depression [13]. A recent meta-analysis of more than 50,000 patients reported that general practitioners in the UK correctly identified depression in less than half (47.3%) of the reported cases [5]. Because of this, many research groups are currently focused on identifying potential biomarkers for both unipolar and bipolar depression that may accurately predict or diagnose patients. Variations in certain genes or in the expression of various alleles are being considered as potential biomarkers, as are epigenetic factors such as histone acetylation and methylation. There are also certain proteins, especially membrane receptors, which are being studied for their potentially predictive role in psychiatric disease development.

Genetic Biomarkers and Depression

Genetic markers are popular targets for study due to the ease of molecular techniques currently available to analyze DNA sequences. A number of studies investigating the genetic basis of depression have uncovered several potentially useful clinical biomarkers, especially among genes that regulate the hypothalamic-pituitary-adrenal (HPA) axis. This is not surprising as the HPA axis has already been implicated in both the development and treatment of depression [14]. It is thought that HPA axis hyperactivity causes insensitivity to inhibition of stress hormones by glucocorticoids. Because glucocorticoid activity is mediated by intracellular receptors, most prominently by the glucocorticoid receptor (GR), a number of studies have hypothesized that GR function and/or number is reduced in patients with depression.

Researchers began by investigating single-nucleotide polymorphisms (SNPs) in various genes that regulate the HPA axis, including NR3C1, the gene that codes for the glucocorticoid receptor, and other co-chaperones of the receptor. They discovered three SNPs related to FKBP5, a gene that codes for an hsp-90 co-chaperone of the glucocorticoid receptor, that were associated with depression [14–16]. Interestingly, individuals with a homozygous expression of one of these

SNPs exhibited an overall increase in depressive episodes and the fastest response to antidepressant medications than those who were heterozygous or were homozygous for a different SNP. One of these three SNPs was discovered by Binder et al., whose research linked genetic variations in FKBP5 to depressive episodes and the uptake of antidepressant medication [14]. The FKBP5 SNPs are currently being investigated further for their predictive value in depression [17, 18]; and stress response [19].

Another genetic marker being studied for its potential role in depression, post-traumatic stress disorder (PTSD), schizophrenia and other psychotic disorders is the BDNF gene, which codes for the neuroprotective protein Brain Derived Neurotrophic Factor (BDNF) [20–22]. BDNF plays an important role in the central nervous system. It is involved in plasticity of synaptic transmission and connectivity of neurons via dendritic branching; it binds with a tyrosine kinase to elicit its neurochemical properties [23]. At the moment, researchers are studying a single base-change mutation – a methionine substitution for valine at codon 66 – for its association with depressive disorders. A 2007 study linked this mutation, often referred to as the val66met SNP, with the development of depression later in life [24]. This study compared elderly patients with depression to age-matched, non-depressed controls, and the results suggested that depressed individuals were significantly more likely to have a methionine substitution at codon 66 than healthy individuals. A second study researching geriatric depression also showed a correlation between the val66met SNP and depression when compared to non-depressed controls [25]. When researchers looked at the correlation of the mutation at codon 66 and depression via analysis with the NEO personality inventory (NEO-PI) questionnaire, they found a strong association between neuroticism – a strong risk factor for depression – and the mutations in the val66met SNP [26]. The Val66Met gene polymorphism appears to enhance symptoms of depression and aggression [27, 28].

A recent genome-wide association study has identified even more significant SNPs by quantitatively modeling patient response to treatment, as measured by the Quick Inventory of Depressive Symptoms (QIDS), in conjunction with the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) genome-wide SNP data [29]. The most significant SNP identified by the researchers was rs11143665, which was located on chromosome 9 (q21.13). This marker, and its neighboring significant markers (rs11143678, rs11143679 and rs11143683), center on a transcript sequence that is expressed in the brain, with rs11143683 located directly in the expressed sequence. Other significant SNPs were found on 18q11.2, 9q21.31, 8q12.1 and 7p12.3, with the majority being located near genes expressed in the brain or linked with neuronal development.

Protein Biomarkers and Depression

Proteomics, the study of protein expression within cells, is a rapidly growing discipline. Since proteins are the end product of genetic expression, studying cell-specific

expression of particular proteins, as well as their concentrations, has yielded several likely biomarker candidates.

One such candidate is the glucocorticoid receptor. As mentioned previously, the glucocorticoid receptor has been widely studied for its potential role in depression and anxiety due to its regulation of stress hormones such as cortisol [30]. Evidence supporting the notion that depressed individuals do not regulate cortisol levels as effectively as non-depressed individuals comes from several different studies. Juruena et al. investigated how well depressed individuals could clear a synthetic form of cortisol called dexamethasone compared to controls. To do this, they used a common diagnostic tool usually employed to detect defects in the HPA axis such as Cushing's disease. Their results showed that non-depressed individuals were able to clear 85% of the synthetic cortisol over a 24-h period while the depressed subjects cleared just 45% [31]. Another interesting result from this study was that prednisolone suppression was similar in both depressed and non-depressed individuals. Prednisolone has similar binding capacity as cortisol, binding to both GR and the mineralcorticoid receptor (MR), while dexamethasone has the highest affinity for GR. These results suggest that, in depressed individuals, GR is the sole receptor with diminished capacity, leading to decreased negative feedback and increased cortisol levels.

The GR receptor also plays a role in treatment efficacy. Carcalho et al. looked at the effects on GR of several different antidepressants versus antipsychotics. Their data showed that various antidepressants affected the glucocorticoid receptor while the antipsychotics did not, suggesting that the antidepressant effect of these drugs are specific for GR [32].

Another protein being studied for its role in the treatment of depression is ATB-binding cassette subfamily B member 1 (ABCB1) also known as multidrug resistance 1 (MDR1). MDR1 is a large transmembrane protein that regulates the crossing of multiple drugs across the blood-brain barrier, including antidepressants. A number of people with major depressive disorder receive no benefit from antidepressant therapy. One hypothesis states that variations in MDR1 do not allow proper passage of antidepressants into the brain. A recent study has shown that seven SNPs in the gene coding for MDR1 were associated with major depressive disorder in Mexican-American subjects [33]. The researchers did not investigate the role these SNPs had on the structure of MDR1; however, they postulated that the SNPs led to changes in the regulation of antidepressants on the blood-brain barrier. More research on this protein is currently under way to elucidate its role in depression development and treatment.

Similarly, the serotonin (5-HT) transporter has been implicated in major depression, bipolar, schizophrenia and other psychotic disorders. Specifically, studies have shown an increased binding or affinity of the 5-HT transporter to lymphocytes and platelets in psychotic patients [34, 35], and a study has even shown that aggressive schizophrenic patients have increased binding over non-aggressive patients [36]. Also, the noradrenaline transporter levels and turnover rate were shown to be significantly decreased in patients with major depression [37].

Metabolomic Biomarkers and Depression

Because of the multi-factorial nature of psychiatric conditions, it is likely that a multi-parameter analysis using a panel of biomarkers or multiple metabolites may produce a more reliable picture of disease diagnosis, prognosis and treatment [38]. Because of this, metabolomic-based approaches to biomarker identification, which examine far-reaching changes in metabolic pathways, are being employed to search for new biomarkers.

Using plasma samples, metabolomic researchers have been able to delineate the biochemical pathways involved in the pathogenesis and treatment response for Major Depressive Disorder. In one such study, blood plasma analysis from 9 depressed, 11 remitted and 10 never-depressed older adults, identified a number of potential new biomarkers [39]. When samples from currently depressed patients and controls were analyzed, alterations were identified in several different fatty acids, glycerol and gamma-aminobutyric acid (GABA). Comparison between remitted and currently depressed patients revealed metabolite alterations similar to those observed between the currently depressed group and controls, as well as high levels of 3hydroxybutanoic acid. These results suggest that depression may be associated with changes in lipid and neurotransmitter metabolism, although more research needs to be conducted to confirm these findings.

Other Biochemical Biomarkers for Depression

There are other well-studied biomarkers of depression, such as elevated levels of the stress hormone cortisol and reduced level of lipids like cholesterol. Hypercortisolemia was first correlated with a depressive psychiatric disorder in 1971 [40]. Studies have since confirmed that hypercortisolemia is a biomarker for depression and determined its pathophysiology [41–45]. This has been one target of depression treatments [46]. Reduced levels of cholesterol, like hypercortisolemia, have long been correlated with depressive disorders [47, 48], and continues to be a focal point for depression research [49, 50].

The stress hormone cortisol is thought to link to depression through its affects on both innate and adaptive immunity. According to a 2009 review, current literature supports the idea that major depression is linked to a pro-inflammatory response, which can be identified by elevated levels of C-reactive protein and cytokines like IL-6 and TNF-α in both plasma and CSF [51]. Other potential inflammatory biomarkers include altered IL-1β levels in CSF, increased thromboxane B2 in plasma and significantly higher levels of PGE2 in saliva [52]. However, the fact that all of these potential biomarkers are only altered in a subgroup of patients severely limits their clinical potential, especially since little research has been done to define subgroups in relation to patients' clinical symptoms.

However, one subgroup of depression patients, those with suicidal intentions, has been studied in terms of pro-inflammatory cytokine levels. In one such study,

non-suicidal patients had elevated levels of IL-6, while suicidal patients had decreased IL-2 [53]. A post-mortem study of suicide victims showed that female victims had increased IL-4 levels and male victims had increased IL-13 levels [54].

Epigenetic Biomarkers and Depression

Epigenetics is the study of heritable changes in phenotype that do not involve alternations in the underlying genetic sequence. While the use of epigenetics in psychiatry is still in its infancy, it holds great promise in explaining some of the mysteries that cannot be explained by looking at genetic sequences. To date, acetylation and methylation are the most studied epigenetic factors, although phosphorylation, ubiquitylation, and sumoylation are also under investigation.

Most studies investigating acetylation have only been conducted in rodents, but key results have shown that increased acetylation of histone H3 on the BDNF promoter leads to decreased depressive symptoms. This study also showed that symptoms could be improved by combining antidepressant therapy with a histone deacetylase inhibitor [55, 56].

A number of studies have identified DNA methylation as a promising biomarker of depression. A small pilot study conducted with depressed adolescents used buccal swabs to look at serotonin transporter gene (5HTT) promoter methylation. This data showed that adolescents with depression had higher levels of promoter methylation than their age-matched, non-depressed counterparts [57]. Another small study examined the brain biochemistry of individuals who had committed suicide and compared them with age-matched controls who had died suddenly from non-psychiatric causes. γ-aminobutyric acid receptor (GABA) was selected for study based on previous data which showed a difference in expression of GABA in suicide victims versus sudden death from other causes. The authors used tissue samples and examined the mRNA of DNA methyltransferase (DNMT), the enzyme responsible for attaching methyl groups to DNA. They found that there were increased amounts of DNMT-3B, which correlated with increased amounts of methylated GABA, in suicide victims but not in sudden-death victims. These data suggest that DNA hypermethylation of GABA may be a contributing factor in major depressive disorder [58].

Neuroimaging and Electrophysiological Biomarkers and Depression

Developments in neuroimaging and electrophysiology technology, especially MRI and electroencephalography (EEG), are providing new opportunities for creating diagnostic and prognostic biomarkers for depression and other psychiatric and CNS disorders. The alterations detected by these methods are mechanistically linked to the causes of these diseases and can, therefore, be considered intermediaries

between the genetic and biochemical origins of depression and its complex physical and psychological symptoms. Presently, neuroimaging in clinical practice has been limited to excluding neurodegenerative disorders in patients presenting with late-life depression.

Using diffusion tensor imaging, Alexopoulos and colleagues demonstrated that microstructural changes in the white matter of multiple frontal limbic brain areas are associated with a poor antidepressant response in geriatric depression [59, 60]. Such white matter abnormalities in the right superior frontal gyrus [61] and dorsolateral prefrontal cortex [62] were found to correlate with late-life depression. This is not surprising as these neuroanatomical areas have been involved in affect regulation circuitry [63], and electroconvulsive therapy and more recently transcranial magnetic stimulation over these brain regions have been successful in treating cases of major depression [64].

Current research has also shown that both wake and sleep EEGs can identify biomarkers of depression as well as antidepressant therapy. For example, prefrontal quantitative EEG cordance appears to predict patient response to antidepressants, while characteristic changes in sleep EEG readings can help identify patients with depression [65]. Based on a number of clinical sleep studies, depressed patients have impaired sleep continuity, disinhibited REM sleep patterns and alterations in non-REM sleep that are visible on sleep EEGs [65].

As we move into the era of personalized medicine, these studies raise the possibility of identify nonresponders to psychopharmacology based on neuroimaging and electrophysiological evidence.

Current Biomarkers for Anxiety

Anxiety is another common but remarkably under-characterized psychiatric disorder. Not surprisingly, the treatment for anxiety is very similar to depression since many of the same underlying mechanisms and neurotransmitters have been implicated in their etiology. A hyperactive HPA axis is thought to be dysfunctional in people who suffer from anxiety as well as depression. However, while the glucocorticoid receptor (GR) is the subject of intense focus for depression researchers, the corticotropin releasing factor (CRF) has gained notoriety among researchers seeking to understand the physiological dysfunctions linked to anxiety disorder.

CRF is released from the hypothalamus where it acts on the pituitary to stimulate the release of adrenocorticotropic hormone (ACTH). ACTH then acts on the adrenal glands to release glucocorticoids, mainly the stress hormone cortisol. Studies have postulated that SNPs in the CRF1 receptor leads to increased amounts of CRF and higher levels of circulating cortisol, which is associated with both anxiety disorder and depression. Because of this, researchers were hoping to establish salivary cortisol tests as a cheap, effective, non-invasive means of establishing a more definitive diagnosis of anxiety disorder. Veen et al. measured salivary cortisol levels in individuals with anxiety disorder and coupled that with questionnaires based on the criteria set forth by the DSM-IV. Their data showed that increased cortisol levels were

associated with symptoms of depression but not anxiety, indicating that anxiety may be more related to sudden stressors than generalized increases in cortisol [66]. Cortisol may prove to be a better biomarker for treatment development rather than diagnosis. Research has shown that antagonists of CRF1, which decrease cortisol production, lead to less stress-induced anxiety in mice [67].

Neuropeptide Y (NPY) is another factor being studied for its role in anxiety. In animals, it is well documented that NPY plays a role in anxiolytic and anxiogenic outcomes depending on the area of expression within the central nervous system [68]. A study conducted in humans sampled individuals that had been victims of the hurricanes in Florida in 2004. Participants were asked to fill out a questionnaire to assess them for general anxiety disorder, especially in relation to hurricanes and the upcoming hurricane season. Participants were also asked to supply a buccal swab for DNA analysis in order to test for a specific SNP in the NPY gene. The results indicated that there was a strong correlation between this SNP and generalized anxiety disorder (GAD), suggesting NPY's role in modulating anxiety manifestations [69]. This was one of the first studies in humans to show a gene-environment correlation by sampling individuals who are at risk for post-disaster GAD via a high stressor such as a hurricane. Another study of NPY in humans showed that individuals expressing the same SNP showed stronger bilateral amygdala activation when exposed to menacing faces, suggesting that this particular SNP again is involved in the manifestation of anxiety disorder [70]. One of the criteria of the DSM-IV is having a heightened state of worry; this may explain why some people who suffer from anxiety are unable to control unnecessary fretting.

All of the related research shows that any of these potential causal agents could easily be developed into a biomarker screening test. What is also clear from genome wide analysis (GWA) is that there are many other genetic loci and proteins to be explored as potential causal agents.

As pharmaceutical and biotechnology companies begin to develop screening tests based on potential biomarkers for depression, anxiety, and other psychiatric disorders, there are still many factors to consider. The first is that there are many other genetic loci and proteins that could play a supporting role in the etiology of these diseases. These conditions are highly multifactorial so a one-size-fits-all approach to testing and diagnosis may not provide the desired results. For example, while many of these disorders are believed to be partly genetic, life experiences and environment also have been implicated in the development of mental illness. Simply taking a buccal swab and telling someone they do or do not express a certain predisposition toward anxiety or depression is not enough for an unequivocal diagnosis. So what would the ideal biomarker be? At this point it is still too early to tell.

Pharmacogenomics

As touched upon in earlier sections, disease biomarkers may also play a role in the effectiveness of treatment. For years, doctors have known that patients have different responses to prescription medication due to genetic variations. With the advancement of microarray analysis, genotyping, and other biotechnologies, a

new field called pharmacogenomics has been born. The idea behind pharmacogenomics is that since every person's metabolism varies, reaction to medication is case dependent; therefore, by identifying subtle genetic differences, doctors could tailor-prescribe dosages, improve the drug's effectiveness and potentially eliminate harmful side effects. This field is of particular interest to researchers studying psychiatric disorders as patients have varying degrees of response to medications. Most often, choosing the best medication is a process of trial and error, with a number of patients never finding relief via pharmaceutical medication.

As awareness of this growing field has increased over the past 7 years, clinicians have adopted more psychiatric pharmacogenomic tests. Initially clinicians were limited to genotyping the cytochrome P459 2D6 gene. Cytochrome P450 is a liver enzyme that is responsible for the metabolism of many drugs, in particular those used in the treatment of anxiety and depression. The high variability of this gene means that patients can have a multitude of responses to medications like paroxetine and fluoxetine that are metabolized through the 2D6 pathway. However, with this test, clinicians can now distinguish between poor and efficient breakdown of these drugs in patients [71].

Newer pharmacogenomic research has focused on the serotonin receptor. Selective serotonin reuptake inhibitors (SSRIs) are one of the most common groups of antidepressants and have variable efficacy. Genotyping studies have shown that people of European descent carry a variant of the serotonin receptor that influences their treatment with SSRIs. As a result, genotyping this receptor can aid clinicians in tailoring dosages for individual patients, much in the same was as cytochrome P459 2D6 genotyping [71].

Despite their clinical usefulness, pharmacogenomic testing is still cost-prohibitive in almost all circumstances. A study investigating the ordering of genotyping by clinicians treating patients for depression found that these tests were ordered approximately 20 times in a 12-month period [72]. Most clinicians only did so for patients who were not responding to medical therapy. So while the idea of personalized medicine is attractive to many, especially those who have suffered for years despite treatment, it will not be feasible until further research confirms its effectiveness.

Ethical Issues Associated with Biomarker Use in Psychiatry

Throughout medical history, certain diagnoses have come with social stigmas attached. These stigmas include, but are not limited to, various plagues, mental retardation, tuberculosis, and HIV. Mental illness is also one of those ailments that people do not want to be associated with; therefore, clinicians are hesitant to "stigmatize" someone by diagnosing them with a psychiatric disorder. This is one of the arguments in favor of more objective, biomarker-based testing. However, as the previously sections have shown, biomarker identification is still in its infancy, and just because one gene or protein is implicated in the disease process does not mean that a test for it will produce the desired diagnostic or predictive results.

Psychiatric disorders are complicated conditions. Not only are they most likely the result of mutations in multiple genes or gene families, but the environment also plays a role in disease etiology. For example, socio-economic status, access to technology, and even religious influence have been shown to modify the onset and severity of psychiatric disorders. This means that introducing genetic biomarker testing can only tell the clinician limited information about the patient's *likelihood* for developing a psychiatric disorder. So someone with a genetic predisposition toward psychiatric disease may not develop symptoms depending on their environmental influences, age, health status, and a myriad of other factors. As a result, it is unwise to make generalizations or predictions based solely on genetic biomarkers. Yet potential screening tests for psychiatric disorders are based only on a single genetic or biochemical biomarker. This fact severely limits their diagnostic and predictive power and raises significant ethical questions.

Is It Ethical to Screen Healthy Individuals for Disorders When They Do Not Have Any Symptoms?

We are currently using genetic screening for susceptibility genes involved in hypercholesterolemia, a risk factor for heart attacks. However, studies have shown that many of the people who test positive for these genes have increased levels of anxiety and worry. After the fact, a small portion of these patients reported that they would have rather not known if they were carriers. A majority, though, did not regret their decision and wanted to know despite the outcome [73, 74].

If a test for depression or other psychiatric disorders becomes available, many people will want to know regardless of the outcome; it is human nature. But will they be able to handle the results? If the results are negative there is a sigh of relief; however, if they are positive in an asymptomatic person, will this alter their life trajectory? Have they been stigmatized, and would this test be the thing that pushes them over the edge? What about parents who want their children screened for this disorder? How would they react to a positive result? That scenario could result in parents who are waiting for the day for their child will start to "hear voices."

On a societal and institutional level, screening non-symptomatic individuals for genetic disorders already has a problematic history. In 2003, a case where a mother was denied insurance for her children because they were carriers of the α_1-antitrypsin gene was reported. This meant that the children were healthy because they carried only one copy of the disease-causing recessive gene, yet family history and genetic testing led to denial of benefits. Following this case, President Bush enacted legislation in 2008 that prohibited insurance companies from denying individuals coverage based on results from genetic testing. This law, known as the Genetic Information Nondiscrimination Act (GINA), also protects individuals from being discriminated against by employers [75].

Insurance companies claim that by not allowing genetic test results to be used for the approval of benefits or to determine premium prices, that it inflates the total

cost of insurance to everyone. According to them, if a person who is predisposed to a genetic condition like familial breast cancer does not disclose this information to the insurance company and subsequently becomes ill, it leads to increased claims and drainage of the system – resulting in a price hike for everyone. The opposing view is that testing positive for familial breast cancer does not guarantee a person will develop the disease, yet by disclosing this information to the insurance company they will be forced to pay increased premiums for their entire life based on an indefinite test result [75]. This type of scenario is referred to as a "moral hazard" by insurance companies [76]. Breast cancer is only one of the pathologies currently being debated; even more convoluted is the area of psychiatry. BRCA analysis is fairly straightforward when compared to what could be available for psychiatric disorders as there is no single genetic, proteomic, or epigenetic causal agent to pin these disorders on.

Today, there is much debate on how legislation should evolve to combat the issues being raised with all of the advances being made in the field of molecular genetics for psychiatric disorders [76]. One problem with the current legislation is that it only covers genetic information; it does not cover diseases that have already manifested. This is of ethical concern because some scenarios are temporary but hold lasting diagnoses. For instance, an unexpected death in a family can lead a person to suffering from a situational depressive episode. The person may work through the bad event and never have an episode again; however, they have been diagnosed with depression. Would this affect their future insurability or subject them to increased premiums? Could a job deny them employment based on this if disclosure was required?

Should Clinicians Test Patients Previously Diagnosed with Depression If They Ask? What If the Test Comes Back Negative?

As mentioned previously, the first biochemical tests for psychiatric diseases are likely to have a lower degree of specificity and validity because of the multifactorial nature of these illnesses. We only need to look at the backlash associated with PPD testing for tuberculosis to get an idea of what could be in store. Not every person who tests positive on a PPD test has an overt infection of TB, yet their name is sent to the health department and they are forced to take 9 months worth of medication. Recent studies have shown that people's lack of knowledge about TB has driven an overt discrimination against TB sufferers [77].

Conclusions and Future Directions

The quest for knowledge and understanding drives scientists, but the ramifications are sometimes not gratifying. Once data is published, it is available for others to use it at their will. The questions are: what will they do and how will it affect the general

public? A manuscript published in June of 2010 touches on many of these issues [72]. It focuses on the concerns of early adopters of serotonin receptor genotyping in depressive patients not responding to medications. Interestingly, some clinicians believe the usefulness of the test is being overstated to patients and the potential results are being overemphasized as the answer to the patient's problem [72].

As more etiological screening tools become available, we must not lose sight of what the medical profession is all about – the patient. Although their DNA or protein profile may help us arrive at a more exact diagnosis or determine optimal dosing, it is the person who has always been and will always be at the heart of our field. Therefore, before adopting any biomarker-based technology into medical practices, it is each physician's responsibility not to get carried away by the hype or the sexy new science and pragmatically evaluate the potential risks and benefits to patients instead.

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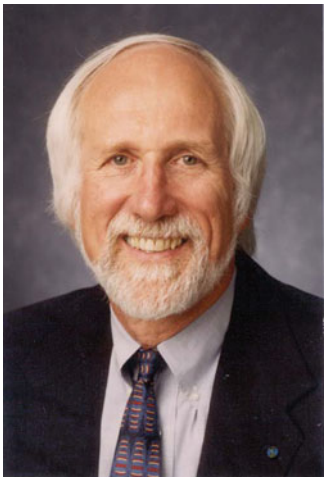
Afterword

William T. Carpenter



The Future of the Schizophrenia Construct and Acquisition of New Knowledge

Professor Ritsner has presented three volumes containing the accumulated knowledge and wisdom developed in the schizophrenia field. Current knowledge is broad and deep, but fundamental challenges remain. Some are as old as Kraepelin's dementia praecox and Bleuler's group of schizophrenias. "What is schizophrenia?" is still a critical question. The construct used to develop new insights and guide clinical therapeutics has a profound effect on study designs, research questions,

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and etiological and therapeutic discovery. In this Afterword I will briefly comment on the current paradigm and speculate on a shift that will substantially change the construct and the methods of acquiring knowledge.

Is the Kraepelinian dichotomy dead? The porous boundaries observed between schizophrenia and bipolar disorders, as presently defined, suggest the answer is yes. However, it is important to appreciate how much the definition of schizophrenia has changed since he proposed a disease entity based on the co-morbidity of avolition and dissociative pathology. Bleuler's postulate that the dissociative pathology was fundamental and primary in all cases, if true, suggested a psychopathological process uniting the various clinical presentations in a single disease concept. However, seemingly without comment, this idea radically changed as Schneider's symptoms of first rank and Langfeldt's true versus pseudo schizophrenia became influential. Movement in the direction of emphasis on ego boundary impairment and reality distortion symptoms became almost universal with the criteria-based DSM-III. Its revolutionary diagnostic standardization required only a single first rank symptom to meet criteria A for schizophrenia and excluded consideration of avolitional pathology as a diagnostic criteria. Described in more detail elsewhere [1], this movement minimized attention to cognitive pathology and negative symptoms. The porous boundary with bipolar disorder observed in genetic and environmental risk factors, neuroimaging, cognition, and response to anti-psychotic drugs is not a test of Kraepelin's concept. Rather, it may represent, at least in part, the heterogeneity of a syndrome based on psychotic features rather than avolition and dissociative pathology. Investigators at the Maryland Psychiatric Research Center have demonstrated substantial differences between schizophrenia patients with the negative symptom pathology compared to schizophrenia patients without primary negative symptoms [2].

It is essential that we recognize the syndrome status of the psychotic disorders including schizophrenia. Doing so immediately raises the challenge of heterogeneity reduction. Does the overlap between syndromes suggest an artificial distinction, or is it indicative of a proportion of patients in each syndrome manifesting similar pathology? For example, depression pathology will be found in almost all bipolar patients, but also in many patients with schizophrenia. A biomarker for depression would be expected to distinguish both groups from non-depressed controls, but may be more robust in bipolar cases. However, including only depressed schizophrenia patients in the schizophrenia cohort could make the difference disappear. This does not suggest that schizophrenia and bipolar are the same disorder. Rather, it suggests that depressive pathology, found in many different diagnostic groups, may be a domain of pathology that merits investigation across diagnostic classes. It would be surprising if, for example, genes associated with vulnerability to depression were not similar in depressed patients from several diagnostic classes. Rather than a genetic marker for a single diagnostic class, this genetic profile could be viewed as marking vulnerability for depression in several discrete disorders and perhaps in the general population as well.

A paradigm shift is essential to maximize progress in the study of schizophrenia. When we recognize schizophrenia as a syndrome, we realize that attempts to define

specific disease entities within the syndrome have not worked with traditional subtypes, but have had some success based on the presence of deficit pathology [2]. Attempts to define dimensions of pathology have been successful. The challenge, then, is to advance the most heuristic approach to deconstructing pathologies associated with syndromes. In the context of the IPSS we put forward a proposal for six pathology domains in 1974 [3], with substantial overlap with the eloquent analysis by Cuesta and Peralta [4] defining eight pathology domains. In the current DSM-V process (I serve as chair of the psychosis workgroup) a series of pathology domains are being considered in addition to diagnostic class. Schizophrenia and other psychotic syndromes would be deconstructed into relevant dimensions representing the pathologies that vary among patients in the diagnostic class and require specific assessment and therapeutic attention. In drug discovery, for example, the paradigm moves away from developing a drug for schizophrenia. Sixty years of producing similar anti-psychotic drugs without discovery for other key domains of pathology illustrates the limited utility of a clinical syndrome. The shift to a deconstruction paradigm defines multiple and separable targets for drug discovery. Therapies for a pathology domain may thereby be effective in multiple diagnostic classes. If this hypothesis is valid, it will transform the developmental pathway for therapeutic discovery. Just as we now have dopamine antagonists with efficacy for psychosis across diagnostic classes, we may come to have a compound or behavioral treatment approved for cognition, avolition, depression, anxiety, and other pathology domains that cross diagnostic boundaries.

DSM-V development is in progress. In addition to the usual diagnostic classes for psychotic disorders, dimensions for anxiety, depression, mania, restricted affect, avolition, cognition, disorganization of thought, delusions, and hallucinations are being field tested. Thus clinical assessments will more closely fit the individual patient's actual pathology and will position the clinician closer to the issues addressed in personalized clinical care. It may also impact future research designs. Rather than genome-wide association study (GWAS) analyses for genes associated with heterogeneous syndromes, the genetics of specific pathological processes will be addressed. Neuroimaging studies may define the structure, function and chemistry associated with specific pathology domains rather than attempting to define biomarkers for syndromes.

This shift in paradigm is relevant for the future study of pathophysiology. The NIMH is developing research diagnostic criteria (http://www.nimh.nih.gov/research-funding/rdoc.shtml) based on neural circuit concepts of symptom expression. For example, a variety of anxiety and mood disorders may relate to pathology in the fear circuitry involving the amygdala and associated structures. NIMH will encourage investigators to investigate neural circuits related to the symptom or impairment of interest, consider phenotype assessment in animal models and recruit patient subjects from the several diagnostic groups associated with the symptom complex of interest. It is hoped that translational science will be advanced by more clearly assessing genotype/phenotype relationships at the level of brain dysfunction where the neuroanatomy and physiology can be "mapped-on" between human and animal models. This involves explicit recognition of the syndrome status of many

psychiatric disorders where deconstruction into component pathologies is essential, and that patients within each syndrome may vary in the domains of pathology with which they are afflicted.

The impact of this paradigm shift will be substantial. Consider the following examples:

- Instead of searching for genes of heterogeneous syndromes, study designs will seek association of genes with neural circuits, phenotypes and specific domains of pathology.
- Drug discovery will target domains of pathology seeking novel compounds for unmet treatment needs such as cognition and negative symptoms associated with some forms of schizophrenia. Efficacy for a specific domain may be relevant to cases in several diagnostic classes where patients manifest the pathology in question.
- Neuroimaging will focus on anatomy, function and chemistry at the intersection of neural circuit and pathology domain rather than the clinical syndrome level.
- Psychosocial treatments will be directed at pathology that cuts across diagnostic boundaries. Instead of broad-based cognitive remediation for schizophrenia, interventions will be tested with subjects who manifest the target impairment. Thus, tailored CBT will address domains such as depressed affect, avolition, or reality distortion rather than major depressive disorder or schizophrenia.

These three volumes speak to the power and the limitations of the dominant model. A paradigm shift, already reflected in some recent studies, promises a new and more robust approach to understand psychopathology and to more specifically addressing the needs of our patients.

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Volume II: Phenotypic and Endophenotypic Presentations

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